LATE RESULTS OF PORTACAVAL ANASTOMOSIS

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THE surgical construction of venous anastomoses, as a means of relieving portal hypertension, has now been practised long enough to justify an assessment of its long-term results. In this department for over ten years the operation of end-to-side portacaval anastomosis has been the procedure of choice in preventing severe hæmorrhage from gastro-œsophageal varices. Earlier results, reported from many centres, have established that this operation is much more effective than splenorenal anastomosis in preventing hæmorrhage, but it has been questioned whether the effect of portacaval anastomosis on liver function and the risk of portal-systemic encephalopathy might not outweigh the advantages of the operation.

More than 150 end-to-side portacaval anastomoses have been performed in this unit. The hospital mortality of this series has been 5·3%, most of the deaths occurring in patients with advanced liver disease who had had severe bleeding which had endangered life. The operative technique employed has already been described (Walker 1959). This paper deals with the long-term results of the first 50 cases; all were operated on more than five years ago and were initially reported by Walker (1957). These patients have now been reviewed with particular regard to survival, recurrent hæmorrhage, state of health, and the development of neuropsychiatric symptoms. The effect of the operation on liver function, size of spleen, œsophageal varices, and " hypersplenism " has also been assessed.

Material and Methods

Of these 50 patients, 15 have died since operation; in all cases their mode of death has been ascertained from hospital or general practitioner, and in all but 4 cases postmortem examinations were performed. 16 of the 35 survivors agreed to return to hospital for detailed assessment carried out over a few days; the remaining 19 have been reviewed as outpatients. The opinion of the general practitioners has also been obtained in the majority of cases.

Selection of Patients for Operation

All 50 patients had proven portal hypertension with œsophageal varices. In the first cases the patency of the portal vein could be shown only at operation; thereafter splenic venography was introduced, and in the remainder the patency of the vein was demonstrated before operation. The obstruction was intrahepatic in all patients, but the degree of structural change in the liver varied widely, ranging from none at all to severe fibrosis and nodularity. All the patients had had hæmatemesis or melæna, except 1 who had a chronic anæmia which was attributed to occult bleeding from varices. It had been the aim to select for operation patients whose liver function was not grossly impaired and who did not show evidence of rapidly progressive disease, judged by their clinical state and liver function. In some cases, however, the operation was undertaken with some reluctance; these showed stigmata of liver-cell failure which was clearly advancing. The risk of a fatal hæmorrhage in these patients was so great that the operation was considered justified. Thus the selection was not so rigid that borderline cases were excluded from the operation if they were likely to die of bleeding. If, however, the operation was indeed contra-indicated because of liver failure or jaundice, then arrest of hæmorrhage was attempted by a transection operation on the stomach or œsophagus (Walker 1960). Of all criteria by which selection for portacaval anastomosis may be made, we place most reliance on clinical judgment: the patient who looks and feels well, apart from his hæmorrhage, usually does well after operation; one who looks ill is likely to have a stormy passage afterwards.

Ætiology of Hepatic Lesion

In common with other reports (Hunt 1958, Sherlock 1960), in the majority of our cases no ætiological factors were found (table I). 5 patients had previously had jaundice, suggesting, though not proving, that viral hepatitis was a cause. Unlike series reported from the U.S.A., chronic alcoholism is not a feature of our cases. This is important, since the prominent clinical features of patients with idiopathic cirrhosis are usually related to portal hypertension. In alcoholic patients, on the other hand, jaundice is much commoner, and their liver function is often much improved by abstinence from alcohol (Summerskill et al. 1960). 2 of the patients had gallstones. In 1 these were removed from the common bileduct and the gallbladder was removed at a preliminary operation; in the other, cholecystectomy was performed at the same time, and this has proved satisfactory in several subsequent cases.

TABLE I—ÆTIOLOGY OF CIRRHOSIS

Cause	No. of cases
Unknown	38
Previous jaundice: viral hepatitis	5
Congenital fibrosis of liver	1
Hepatolenticular degeneration	1
Hæmochromatosis	2
Chronic alcoholism	2
Schistosomiasis	1
Total	50

Age

The ages at the time of operation are shown in table II. The youngest patient, aged 5 years, had congenital fibrosis of the liver (Kerr et al. 1961). In view of the increased risk of venous thrombosis in older patients, considerable caution was exercised in recommending the operation in patients over the age of 55.

Results

Hospital Mortality

Of the 50 patients 3 died in hospital after operation from liver failure and hepatic coma, giving a mortality of 6%. In 1, whose shunt was occluded at necropsy, much recent clot had been removed from the portal vein at

TABLE II—AGES AT OPERATION

Age at operation (yr.)	No.
0–9	1
10–19	7
20–29	15
30–39	15
40–49	9
50–59	3
Total	50

Of the 50 patients 31 were male and 19 female. The youngest patient was aged 5 years and the oldest 57.

operation. These 3 patients had bled many times and 1 had received over 60 pints of blood before coming to operation.

Subsequent Deaths

12 patients died subsequently, 4 from causes unrelated to their cirrhosis, while 8 eventually succumbed to liver failure (table III). Of these patients, who died at times varying between four months and four years eleven months after operation, 2 had had recurrence of bleeding. In 1 of these the hæmatemesis, seven months after operation, was severe and death may be largely attributed to it. This patient was a man who had undergone a splenorenal anastomosis two years before portacaval anastomosis. At necropsy the splenic vein was thrombosed, but the portacaval shunt was patent. The other patient died from a ruptured aortic aneurysm two years after portacaval anastomosis, slight bleeding having taken place in the first postoperative month.

Survivors

35 of the 50 patients—that is, 70%—have survived more than five years, and there have, so far, been no deaths after more than five years. These 35 cases we have initially classified as follows:

Grade I.—No symptoms, no recurrent bleeding. At full work.

Grade II.—No recurrent bleeding. Symptoms minimal and such that the patient does not feel it necessary to consult a doctor repeatedly. At full work.

Grade III.—Symptoms troublesome; has consulted doctor repeatedly, may have been admitted to hospital. On and off work.

Grade IV.—Symptoms severe and indicative of rapidly advancing liver failure.

The symptoms experienced include general deterioration of health, anorexia, easy fatiguability, loss of weight, attacks of hepatic coma or jaundice, swelling of the ankles, and ascites. Such symptoms are well-recognised manifestations of hepatic failure. Epistaxis, a minor symptom, occurred in 9 of the 35 survivors.

Table IV shows the distribution of patients according to this classification. 29 of the 35—i.e., 83%—are at work earning their living or, in the case of the women, can perform household duties. It will be seen later that the liver function in these 29 cases has remained adequate since operation. In effect, then, the follow-up of these patients gives a picture of the natural history of portal cirrhosis, which is so slowly progressive that it merits the term quiescent.

Recurrent Hæmorrhage

6 patients had some recurrence of bleeding, and 2 such instances have been described above. The other 4 patients are still alive. In 2 the recurrent bleeding was minor and did not require transfusion. They bled in their first postoperative year and have since survived, free from hæmorrhage, to reach six years and seven years after operation. The remaining 2 patients who bled again had both undergone splenectomy some time before portacaval shunt was performed. The decompression of the portal system achieved in these 2 cases appears inadequate, since, despite a patent shunt, œsophageal varices persisted, and in each case a " transection " operation was subsequently performed. Both patients survive, one to seven years and the other to ten years.

The 12% rate for recurrent bleeding contrasts strikingly with the number of hæmorrhages before operation. Before shunt 150 episodes of bleeding had occurred in the group as a whole. After shunt, 10 episodes have occurred in the 6 cases discussed above.

Thrombosis of the Shunt

This has been verified at necropsy in only 2 cases. In 1 it was occluded by a carcinoma of the pancreas; in the other, recent thrombus was removed from the portal vein at operation, but recurred and was found at necropsy seven days later. In a 3rd patient, who survives to her eighth year after operation without recurrent bleeding, the shunt has probably closed. In this case splenomegaly and varices disappeared postoperatively, but returned at three years. Since the patient remains well, percutaneous splenic venography, which would clarify the position, has not been performed.

TABLE IV—DISTRIBUTION OF CASES ACCORDING TO SEVERITY OF POSTOPERATIVE DISORDER

—	Years postop.						Total
	6	7	8	9	10	11	
No. of cases in each year	9	8	5	4	8	1	35
Grade:							
I	5	5	1	2	1	1	15
II	2	2	3	1	6	0	14
III	2	1	1	1	1	0	6
IV	0	0	0	0	0	0	0

In the remaining cases the shunts are presumed to be patent. We do not consider it justifiable to perform splenic venography on patients as a follow-up investigation five or more years after operation when they are well. Instead, evidence that the shunt is still patent is obtained by continued absence of splenomegaly and of œsophageal varices on barium swallow.

Mural Thrombus at Operation

At operation 11 patients were found to have some degree of thrombosis in the portal vein; these included the 2 patients whose spleens had been removed previously and the patient who had an occluded splenorenal anastomosis.

TABLE III—DATA ON PATIENTS WHO DIED POSTOPERATIVELY

Case no.	Age at operation (yr.)	Ætiology of cirrhosis	Cause of death	Time postop.	State of shunt at necropsy
Early deaths:					
1	32	Idiopathic	Hepatic coma	15 days	Patent
2	38	,,	,, ,,	5 weeks	,,
3	45	,,	,, ,,	7 days	Closed
Late deaths:					
4	40	,,	Rupture pyosalpinx	4 mos.	Patent
5	33	,,	Hepatic failure	7 mos.	Patent but splenic vein thrombosed (previous splenorenal anastomosis)
6	45	Hæmochromatosis	,, ,,	1 yr. 9 mos.	..
7	55	Viral hepatitis	Aortic aneurysm	2 yr.	Patent
8	39	Alcohol	Hepatic failure	2 yr. 4 mos.	,,
9	35	,,	,, ,,	2 yr. 8 mos.	,,
10	19	Viral hepatitis	,, ,,	2 yr. 8 mos.	,,
11	17	Hepatolenticular degeneration	,, ,,	2 yr. 9 mos.	,,
12	55	Idiopathic	Cardiac failure	2 yr. 9 mos.	..
13	44	,,	Pancreatic carcinoma	4 yr.	Occluded by carcinoma
14	38	,,	Hepatic failure	4 yr. 1 mo.	..
15	12	,,	,, ,,	4 yr. 11 mos.	..

In 7 the clot was not recent and was represented by firm plaques on the vein wall which were completely covered by endothelium; these were not disturbed at the operation, but they made the suturing of the anastomosis more difficult. 2 of these patients died while still in hospital, 1 with his shunt closed; another died four years later with the anastomosis occluded by carcinoma, but in the other 4 the anastomosis remains patent.

In 4 cases the clot was recent, and some or all of it was removed before the anastomosis was made. 3 of these patients are alive and the evidence is that their shunts are still open; the 4th died eight months later, but his anastomosis was fully patent.

Size of Spleen: "Hypersplenism"

In 70% of the patients the spleen shrank after operation to become impalpable. In the remainder the spleen was considerably smaller than before operation, but still palpable. The diminution in size invariably began in the first postoperative week and often continued for months. Splenomegaly returned in the presence of a patent shunt in 2 patients when the terminal stages of liver failure developed. Since the patency of the shunt was verified at necropsy in these 2 cases, the splenomegaly was presumably due to a cause other than portal congestion, possibly reticuloendothelial hyperplasia. The hæmatological changes of "hypersplenism" persisted after operation. Before operation 80% of patients had a platelet-count of less than 200,000 per c. mm. and in 50% the count was below 100,000 per c. mm. Between five and ten years later the platelet-count whenever performed was below 200,000, and in 40% it was below 100,000 per c. mm. Fig. 1 shows the trend of platelet level with passage of time. The level of circulating white blood-cells tended to follow the same course as the platelets, and 41% of patients had a white-cell count of less than 3000 per c. mm. at operation.

It has, however, never been felt necessary to perform splenectomy after portacaval anastomosis, since the hæmatological features of "hypersplenism" are unaccompanied by any troublesome symptoms. Epistaxis, as mentioned before, occurred in 9 of the 35 survivors. One patient, however, a case of hæmochromatosis, required splenectomy fifteen months after operation on account of severe hæmolytic anæmia.

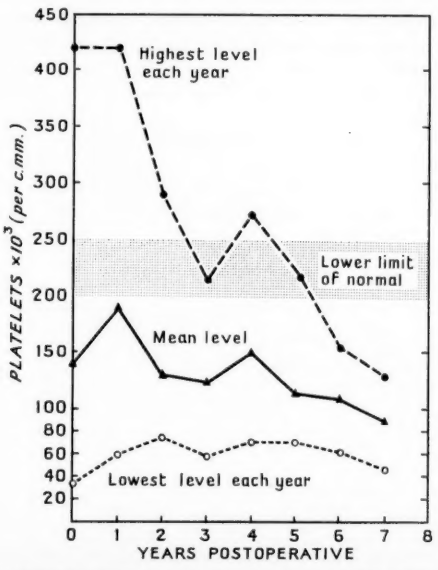

Fig. 1—Platelet-counts in each of seven postoperative years.

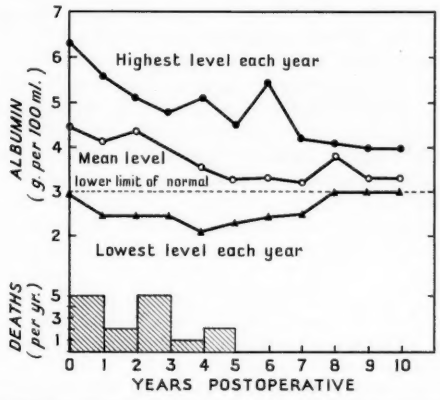

Fig. 2—Serum-albumin levels and deaths in each of ten postoperative years.

Oesophageal Varices

Disappearance of oesophageal varices, judged by barium swallow, occurred in 89% of cases examined. In the remaining 11% the varices, although present, were smaller in extent and size than before operation.

Liver Function

At the time of operation 94% of patients had a serum-albumin level of more than 3 g. per 100 ml. Fig. 2 shows the level of serum-albumin plotted against years after operation. After five years the mean level is steadily maintained above 3 g. per 100 ml. Of the 15 patients who died 11 succumbed to liver failure in the first five years; after this period no deaths have occurred and liver function, judged by serum-albumin, remains at about the same level as before operation.

The serum-bilirubin level was normal (0–1 mg. per 100 ml.) at the time of operation in 31 of the 35 patients who have survived more than five years. At the time of follow-up 19 of the 31 still had normal levels, but in 12 patients the serum-bilirubin rose to 1–3 mg. per 100 ml. in the first two years after operation and has persisted at these levels.

4 patients were operated on with a serum-bilirubin of 1–3 mg. per 100 ml., and in each instance this level has persisted through the years.

Of the 15 patients who died, 3 had a serum-bilirubin level between 1 and 3 mg. per 100 ml. at operation, while at the time of death 10 out of 15 had levels varying between 2 and 12 mg. per 100 ml. Thus the operation of portacaval anastomosis has not resulted in any significant degree of jaundice in the patients who survived more than five years.

Liver Structure

In 12 of the patients who were reviewed in hospital, percutaneous needle biopsy of the liver was performed. Comparison of the histological features of these biopsy specimens with those taken at operation revealed little evidence of any increase or decrease in the three histological features of cirrhosis—namely, cellular necrosis, regeneration, and fibrosis.

Ascites

At operation the presence of ascites was verified in 10 of the 50 cases. The amount of ascitic fluid varied considerably from patient to patient, but in each case was detectable clinically. 3 of the 10 patients have died from

liver failure, but the other 7 remain alive and well and have had no recurrence of ascites since operation.

Portal-systemic Encephalopathy (P.S.E.)

This complex syndrome is now recognised as a complication of shunt surgery. In our experience its manifestations have been most varied and have included features varying from disturbance of conscious level, changes in personality, neurological disorders, deterioration of intellect, and slow slurred speech to coma. Of this series of 50 cases evidence of one or more of these features has been observed in 10—a rate of 20%. The patients are classified thus:

(1) 11 *patients who have died of liver failure.*—2 of these patients had recurrent attacks of P.S.E. before their terminal illness. In the other 9 patients hepatic coma was terminal, and they are not included in the rate for P.S.E.

(2) 15 *patients classified in grade I* (table IV.—Only 1 of these patients had P.S.E. In this case drowsiness and tremor developed three weeks after operation, but there has been no subsequent recurrence of the syndrome.

(3) 14 *patients included in grade II* (table IV).—In 2 of these patients P.S.E. has occurred. In 1 attacks of drowsiness developed eighteen months after operation and recurred for three years, but since partial gastrectomy on account of chronic duodenal ulcer the frequency and severity of his symptoms have surprisingly lessened. In the other case clinical evidence of P.S.E. began to appear six and a half years after operation. However, this man still works as a school inspector and an amateur music conductor nine years after operation.

(4) 6 *patients included in grade III* (table IV).—In 5 of these patients P.S.E. is recurrent and all are severely incapacitated by its manifestations.

Thus, although 10 patients have experienced P.S.E. at one time or another after operation, in only 5 was the syndrome incapacitating to any extent. Only 1 patient younger than 35 at the time of operation has developed P.S.E., despite the wide age range of the whole series of 50 cases. P.S.E. is still unexplained; but we have found that the syndrome may be precipitated, not only by large protein meals, but also by constipation and that it often accompanies a period of deterioration in liver function.

Summary

The results of 50 operations of end-to-side portacaval anastomosis, performed between five and eleven years ago, have been reviewed. The operations were undertaken to prevent recurrent hæmorrhage in patients with portal hypertension due to intrahepatic obstruction.

3 patients died while still in hospital; 12 others died subsequently, 4 from unrelated diseases. 35 patients have survived for more than five years, after which time no deaths have as yet occurred.

Of the 35 survivors, 5 are severely incapacitated by portal-systemic encephalopathy; 29 of the remaining survivors lead normal lives, and 15 of these are sympton-free.

Recurrent hæmorrhage was very unusual after the first postoperative month.

Although leucopenia and thrombocytopenia persisted, they did not cause any incapacity.

The liver function of the survivors, judge dclinically and biochemically, is well maintained after five years; and ascites, when present at operation, has not recurred in any case.

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CHANGES IN FIBRINOLYTIC ACTIVITY PRODUCED BY PHYSICAL ACTIVITY

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I. EFFECT OF MODERATE EXERCISE

SEVERAL studies have shown that short periods of exercise substantially increase blood fibrinolytic activity (Biggs et al. 1947, Truelove 1953, Fearnley and Lackner 1955, Sherry et al. 1959, Billimoria et al. 1959, Sawyer et al. 1960). Our study was undertaken to extend these findings.

Methods

Plasma fibrinolytic activity was determined by a modification of Bidwell's method (1953). Blood and plasma specimens were kept in melting ice, and all glassware was cooled before use. The concentration of thrombin employed was 5 units per ml. Incubation of the clots was commenced half an hour after venepuncture. An estimation of the fibrin content of the clot was made after incubation for 30 minutes—i.e., before the beginning of lysis. Estimations of the residual fibrin were made after 2, 4, 8, and 24 hours. All estimations were performed in triplicate. The collection of clots on glass rods was found unsatisfactory. 'Tyglas' (Fothergill & Harvey Ltd.), as suggested by Billimoria et al. (1959), was used to obtain a complete yield of fibrin.

The subjects of the experiments were healthy young adults aged between 20 and 30. All experiments were carried out in the morning after a normal breakfast, which in our experience does not significantly alter fibrinolysis, and the subjects abstained from strenuous exercise before the tests. In addition they rested for 30 minutes before the initial venepuncture. In all the following experiments, the exercise entailed walking at 4 miles an hour for varying periods.

Results

Table I presents the results in ten subjects who walked 4 miles in one hour, blood being obtained before and immediately after the exercise. In all subjects fibrinolysis considerably increased. The three females had a greater fibrinolytic response, but the numbers are not sufficient for separate analysis.

The next part of the investigation was undertaken to determine whether fibrinolytic activity rose proportionately with the amount of exercise. Five subjects walked 4 miles in one hour, venous blood samples being obtained before the exercise, after 2 miles, and after 4 miles.

TABLE I—EFFECT OF WALKING 4 MILES IN 1 HOUR

Subject and sex	Before exercise				After exercise			
	% lysis after				% lysis after			
	2 hr.	4 hr.	8 hr.	24 hr.	2 hr.	4 hr.	8 hr.	24 hr.
1 F	0	3·5	34	100	60·5	100	100	100
2 M	0	0	7	60·5	13	50	100	100
3 M	0	0	16	39	11	70·5	100	100
4 M	0	14·5	71·5	100	20	76·5	100	100
5 M	0	0	19·5	100	0	48	100	100
6 M	0	0	21·5	100	9·5	86	100	100
7 F	0	0	26·5	100	58	100	100	100
8 M	0	17·5	95	100	10	95	100	100
9 F	0	15·5	50	100	16·5	98	100	100
10 M	0	0	17	94·5	4	46	100	100
Mean	0	5·1	35·8	86·4	19·3	76·8	100	100

TABLE II—EFFECT OF WALKING 2 MILES COMPARED WITH EFFECT OF WALKING 4 MILES

Subject and sex	—	% lysis after			
		2 hr.	4 hr.	8 hr.	24 hr.
1 M	Before ..	0	0	7	60·5
	After 2 miles	0	10	43·5	100
	After 4 miles	13	50	100	100
2 M	Before ..	0	14·5	71·5	100
	After 2 miles	11	41	97·5	100
	After 4 miles	20	76·5	100	100
3 M	Before ..	0	0	19·5	100
	After 2 miles	0	25·5	96	100
	After 4 miles	0	48	100	100
4 M	Before ..	0	17·5	95	100
	After 2 miles	8	72	100	100
	After 4 miles	10	95	100	100
5 M	Before ..	0	0	17	94·5
	After 2 miles	0	20	100	100
	After 4 miles	4	46	100	100
Means	Before ..	0	6·4	41·8	91
	After 2 miles	4	33·7	87·4	100
	After 4 miles	9·6	63·1	100	100

Table II shows that during this period of exercise the fibrinolytic activity rises proportionately with the duration of exercise.

A further three subjects walked 12 miles at the same speed as those in the previous experiment. Table III shows some variation in the pattern of fibrinolytic response, but apparently there was no proportionate increase in fibrinolysis after 2 hours of this exercise (8 miles). Two of the subjects actually showed a slight fall in fibrinolytic activity between 2 and 3 hours.

The duration of the fibrinolytic response after a period of exercise has also been studied. The subjects walked 2 miles in 30 minutes, after which they rested for an hour. Blood samples were obtained before and after the period of exercise and after completion of the rest. The same experiment was repeated except that 4 miles were walked in one hour. Table IV shows that the fibrinolytic activity had not returned to the basal level in any of the subjects after an hour's rest, although the major part of the increased fibrinolysis produced by exercise had disappeared. It may also be seen that slightly greater fibrinolytic activity persists after rest for 1 hour when the period of exercise is increased from a half an hour to an hour.

Discussion

The increasing attention paid to the physiological mechanisms controlling fibrinolysis partly results from the suggestion that impaired fibrinolysis may play a part in the pathogenesis of atheroma (Astrup 1959), and in the formation of occlusive intravascular thrombi.

Epidemiological studies have implicated lack of physical activity as a factor in the ætiology of ischæmic heart-disease, in particular coronary thrombosis (Morris and Crawford 1958), and the effect of physical activity on fibrinolysis is one way in which this association might be explained.

The results of this study have confirmed that plasma fibrinolytic activity is substantially increased by moderate exercise. Sherry et al. (1959) have convincingly demonstrated that the increased fibrinolytic activity following exercise is due to the appearance of more plasminogen activator in the circulation. The fact that a considerable part of this increased fibrinolytic activity has disappeared after resting for an hour (see table IV) suggests that the circulating activator is fairly rapidly destroyed or neutralised. Thus short periods of exercise at long intervals are of little value in maintaining a high fibrinolytic potentiality in the blood.

The results of increasing the duration of physical activity beyond 2 hours (see table III) suggest that the body achieves a maximum fibrinolytic response to this particular stimulus, which is not increased by prolonging the application of the stimulus. Accordingly studies have been undertaken to assess the effect of physical activity for longer periods.

The part of this study so far recorded suggests that, if the fibrinolytic mechanism has a role in the prevention of coronary-artery disease, moderate physical activity, frequently repeated, is of importance.

TABLE III—EFFECT OF WALKING 12 MILES IN 3 HOURS

Subject and sex	—	% lysis after			
		2 hr.	4 hr.	8 hr.	24 hr.
1 F	Before ..	0	8·5	44·5	100
	After 4 miles	71	100	100	100
	After 8 miles	72	100	100	100
	After 12 miles	47	100	100	100
2 M	Before ..	0	0	21·5	100
	After 4 miles	9·5	86	100	100
	After 8 miles	54·5	100	100	100
	After 12 miles	19·5	94	100	100
3 F	Before ..	0	15·5	50	100
	After 4 miles	16·5	98	100	100
	After 8 miles	40	100	100	100
	After 12 miles	46·5	100	100	100

II. EFFECT OF PROLONGED EXERCISE

The following experiments were undertaken to assess the effect on fibrinolysis of several hours' physical activity, and the alteration after this activity was discontinued.

Methods

Plasma fibrinolytic activity was determined as described above.

Streptokinase-activated lysis-time.—This method consists essentially of measuring the rate of lysis of a plasma clot in the presence of excess streptokinase. It is based on the fact that streptokinase, together with a substance present in human plasma (proactivator), forms a potent activator of plasminogen.

TABLE IV—EFFECT OF REST FOR 1 HOUR AFTER WALKING 2 MILES AND 4 MILES

Subject and sex	2 mile walk											
	Before exercise				After exercise				After rest			
	% lysis after				% lysis after				% lysis after			
	2 hr.	4 hr.	8 hr.	24 hr.	2 hr.	4 hr.	8 hr.	24 hr.	2 hr.	4 hr.	8 hr.	24 hr.
1 M	0	0	11·5	94	0	45	100	100	0	3·5	42	100
2 M	0	0	25	93·5	13·5	88·5	100	100	0	44	100	100
3 F	0	4	24·5	100	22·5	95·5	100	100	0	14	58	100
4 M	0	35	100	100	60	100	100	100	14	84·5	100	100
	4 mile walk											
2 M	0	0	16	39	11	70·5	100	100	8	57·5	100	100
3 F	0	0	26·5	100	58	100	100	100	0	14·5	79·5	100
5 M	0	15·5	40·5	100	..	100	100	100	0	28·5	89	100
6 F	0	3·5	34	100	60·5	100	100	100	0	28	100	100

If excess streptokinase is used, a deficiency of either pro-activator or plasminogen will reduce the amount of plasmin formed and therefore the speed of clot lysis. Prolongation of the lysis-time, however, may also imply inhibition of the activation of proactivator or plasminogen.

The streptokinase-activated lysis-time was estimated by adding 0·2 ml. of oxalated plasma to a mixture of 0·1 ml. streptokinase (2000 units per ml. in buffered saline, pH 7·4), 0·1 ml. thrombin (20 N.I.H. units per ml.), and 0·2 ml. buffered saline in a glass tube (3 in. × $^3/_8$ in.) in a water-bath at 37°C. A stopwatch was started at the moment of clotting and the time of clot lysis was noted, taking the release of air bubbles within the clot as the end-point.

TABLE V—FIBRINOLYTIC ACTIVITY IN 6 SUBJECTS AT THE SAME TIME ON DIFFERENT DAYS WITH EXERCISE AND DIET CONSTANT

Subject	Day	% lysis after		
		4 hr.	8 hr.	24 hr.
1	1	9	55	100
	2	4	42	100
	3	10	56	100
2	1	16	72	100
	2	13	64	100
3	1	0	0	7·5
	2	0	0	5
4	1	5	49	100
	2	8	49·5	100
	3	8·5	44·5	100
5	1	8	21·5	100
	2	0	21·5	100
6	1	0	10	60·5
	2	0	9·5	40
	3	0	8	76

Three standard patterns of prolonged exercise were used in this study:

Exercise I—Walking to a height of 3800 feet over rough paths and heather. The distance walked was about 14 miles and required some 6 hours to complete.

Exercise II—Walking on snow over hilly country for 5 hours.

Exercise III—Walking 12 miles in 3 hours on pavements.

All the subjects were healthy young adults, aged between 20 and 30.

Results

Table V illustrates that, when such variables as time of day, exercise, anxiety, and diet are carefully controlled, only minor day-to-day variation in fibrinolytic activity occurs. In the following experiments, in all comparisons between the fibrinolytic activities on different days, these criteria were rigidly controlled.

TABLE VI—EFFECT OF EXERCISE I

Subject	After day of exercise				After normal day			
	% lysis after				% lysis after			
	4 hr.	8 hr.	12 hr.	24 hr.	4 hr.	8 hr.	12 hr.	24 hr.
1	0	23	66·5	100	6	65·5	100	100
2	0	0	41	100	8	64	100	100
3	0	0	0	31	6	50	100	100
4	0	14	39·5	86	12·5	40·5	90	100
5	0	60	96	100	34·5	96·5	100	100
Means	0	15·4	44·6	83·4	13·4	63·3	98	100

Table VI summarises the results in five subjects who undertook exercise I. Blood was obtained on the morning after this exercise, some 14 hours after its completion, and on a subsequent morning after a day of normal activity. All five subjects showed a depression of plasma fibrinolytic activity on the day after the prolonged exercise compared with the control morning. This amount of physical activity induced considerable fatigue in all these subjects.

TABLE VII—EFFECT OF EXERCISE II

Subject	3 hours after exercise			Control day		
	% lysis after			% lysis after		
	4 hr.	8 hr.	24 hr.	4 hr.	8 hr.	24 hr.
1	57	100	100	34	100	100
2	51	100	100	33·5	100	100
3	71	100	100	21·5	100	100
4	49	100	100	50·5	100	100
	Morning after exercise			Control morning		
5	0	8·5	80	0	11·5	55
6	8	37	100	26	97·5	100
7	3	13	32	23·5	95·5	100

To determine whether this depression of fibrinolysis occurred soon after the completion of prolonged exercise, a further group of subjects undertook exercise II.

Blood was obtained from four subjects 3 hours after the completion of the walk, and from three further subjects on the morning following the exercise. Control estimations were performed on blood withdrawn at the same times on subsequent days. It can be seen from table VII that 3 hours after the exercise there was a slight increase in fibrinolytic activity as compared with the control day in three of the four subjects, while two of the three subjects from whom blood was obtained the following morning had substantially less fibrinolytic activity than on the control day. It is of interest that subject 5, who showed no such depression was accustomed to long periods of physical exertion and was not appreciably fatigued by this amount of exercise. This is in contrast to all the other subjects who showed a depression of fibrinolysis on the morning after a day of strenuous exercise.

It is apparent, therefore, that prolonged exercise causes an increase in fibrinolytic activity 3 hours after the exercise is discontinued, but in untrained subjects it falls next day to levels below those found on "control" days.

TABLE VIII—FIBRINOLYSIS AND STREPTOKINASE-ACTIVATED LYSIS TIMES BEFORE, ONE AND TWO DAYS AFTER EXERCISE III

Subject	Day	% lysis after				Streptokinase-activated lysis time (sec.)
		2 hr.	4 hr.	8 hr.	24 hr.	
1	0	0	8·5	44·5	100	60
	1	0	0	3	57·5	62
	2	0	13	37·5	100	60
2	0	0	15·5	50	100	52
	1	0	0	16	92·5	52
	2	0	12·5	66	100	..

Fletcher et al. (1959) have shown that the intravenous administration of large doses of streptokinase results in a depletion of circulating plasminogen. They have also shown that plasminogen-depleted clots lyse slowly even in the presence of large amounts of activator (Alkjaersig et al. 1959). We thought that depletion of plasminogen, due to its conversion to plasmin by activator liberated during exercise, might be the explanation of the depression of fibrinolytic activity following prolonged exercise. Accordingly the streptokinase-activated lysis-time, which would

TABLE IX—RESPONSE OF FIBRINOLYTIC ACTIVITY TO MODERATE EXERCISE (2 MILES) DURING AND ON THE DAY FOLLOWING PROLONGED EXERCISE

—	—	% lysis after			
		2 hr.	4 hr.	8 hr.	24 hr.
Day 0	Before exercise (18 miles)	0	9·5	43·5	100
	After walking first 2 miles	22·5	95·5	100	100
Day 1	Before exercise	0	6	23	100
	After walking 2 miles ..	8·5	27	95	100

be lengthened by plasminogen depletion, was estimated on the plasma of two subjects showing a depression of fibrinolysis on the day after a walk of 12 miles (exercise III). Table VIII shows that the streptokinase-activated lysis-times have not altered in the presence of depressed plasma fibrinolytic activity, and we may conclude that plasminogen depletion is not the reason for the fall in plasma fibrinolytic activity following prolonged exercise. It may be noted that the lowered fibrinolytic activity has returned to its normal level by the succeeding morning.

A further possibility seemed to be that the reduction in fibrinolysis on the day after prolonged exercise is due to appearance of an anti-activator in the circulation in response to the presence of large amounts of activator over an unusually long period of exercise. This hypothesis has been explored, at present, only in one subject. This subject walked a distance of 18 miles in three periods of 6 miles in the course of some 10 hours. Blood was obtained before the commencement of this exercise, after completing 2 miles in 30 minutes, and next morning. After this third venepuncture the subject walked 2 miles in 30 minutes, and a further sample of blood was withdrawn. Although the depression of fibrinolytic activity on the morning after the prolonged exertion was less than usual, the response to a 2-mile walk was very substantially reduced on this day (see table IX). Although suggestive, this single observation cannot be taken as conclusive proof that an anti-activator is produced.

Discussion

In the previous experiments we showed that short periods of physical activity result in a considerable, though transient, increase in plasma fibrinolytic activity. If the hypothesis that the fibrinolytic mechanism has a role in the prevention of coronary artery disease is correct, moderate physical activity can be assumed to be beneficial. Our observation that long and strenuous exercise in untrained subjects has a delayed depressing effect on fibrinolytic activity suggests that sustained physical effort may harm those unaccustomed to it. It would be interesting to know whether this depression of fibrinolytic activity by exercise increases with age.

The concept that the presence of large amounts of plasminogen activator in the circulating blood over long periods results in a later "rebound" in fibrinolytic activity leads to speculation about other stresses which increased fibrinolytic activity by stimulating release of activator into the circulation. Mental stress has been found to increase fibrinolytic activity (Macfarlane and Biggs 1946, Truelove 1951), and Sherry et al. (1959) have shown that this is due to the appearance of plasminogen activator in the circulation. There is some epidemiological evidence that mental stress is linked with coronary-artery disease (Russek and Zohman 1958, Friedman and Rosenman 1959) and it is possible that long periods of mental stress may contribute to coronary-artery disease by causing a later depression of fibrinolytic activity. However this must remain speculative until experimental evidence is produced.

SUMMARY

Short periods of moderate physical exercise increase the fibrinolytic activity of the plasma. At first, fibrinolysis rises proportionately with the amount of exercise, but, as the period of exercise lengthens, fibrinolysis does not continue to increase.

After short periods of moderate exercise, fibrinolytic activity is still above normal after an hour's rest. After longer periods of exercise it is higher still.

Plasma fibrinolytic activity is below normal on the morning after several hours' exercise by untrained subjects.

This depression is not due to plasminogen depletion. The role of an anti-activator in its production is postulated.

Our thanks are due to the subjects who took part in experiments, which were both time-consuming and arduous.

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THE CEREBRAL COMPLICATIONS OF PULMONARY ALVEOLAR PROTEINOSIS

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CASES of pulmonary alveolar proteinosis have been recognised with increasing frequency since the entity was first described by Rosen, Castleman, and Liebow in 1958. Over sixty examples have now been published, of which about a quarter had proved fatal. In the following case the clinical details and the establishment of the diagnosis have already been reported (Hall 1960), but an account of the terminal illness and necropsy findings may be useful because a difficult neurological diagnostic problem developed, caused by unusual complications.

Case-report

A man aged 36 gave a 2-year history of increasing breathlessness with diffuse shadowing on the chest radiograph. 15 months after the onset of symptoms a lung biopsy (April 28, 1959) showed that he had pulmonary alveolar proteinosis. Treatment with prednisone had been given but was discontinued before the biopsy because it appeared to be ineffective.

Over the next 8 months, without any treatment, the dyspnœa remained fairly constant although the X-ray changes increased. In January, 1960, he began to get attacks in which his legs suddenly collapsed, and in which he had headaches and a feeling of muzziness without true vertigo. The headaches gradually got more frequent and severe, especially in the early hours of the morning, and they were made worse by lying or bending down and by coughing. About a month later he developed diplopia, slurring of speech, and nausea. In the subsequent 3 weeks unsteadiness and weakness of the left arm were manifest and the left side of the face felt numb. He began to vomit, and walking was difficult because of vertigo. He became lethargic, pyrexial, and incontinent of urine.

Final Admission

When admitted to the department of neurology, Royal Hospital Annexe, Sheffield, on March 30, 1960, under the care of Dr. J. P. P. Bradshaw, he was drowsy, dyspnœic, pyrexial,

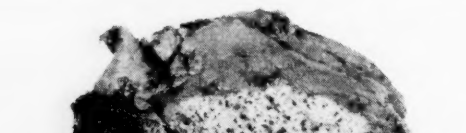

Fig. 1—Section of left lung showing consolidation with yellow material predominantly in upper lobe.

and extremely wasted. There was moderate finger clubbing. His respiratory rate was 30 per min. Numerous crepitations were heard over both lung fields, with occasional expiratory rhonchi, but the percussion note was not impaired. The heart appeared normal and the blood-pressure was 120/80 mm. Hg.

On neurological examination, there was bilateral papillœdema with no diminution of the visual fields. Nystagmus on looking to the left, bilateral ptosis, failure of upward gaze, and a left external rectus palsy were noted. The left side of the face was numb, although the corneal reflexes were equal. There was left-sided facial and palatal weakness with a left hemiplegia and ataxia. The reflexes on the left side were accentuated, with an extensor plantar response.

A blood-count showed 3·7 million red cells per c.mm. with a hæmoglobin of 84% (12·4 g.) and 13,400 white cells per c.mm. (87% neutrophils). The erythrocyte-sedimentation rate (Westergren) was 112 mm. in the first hour. The serum electrolytes were normal apart from a slightly raised chloride of 110 mEq. per litre. The serum-albumin was 3·6 g. per 100 ml.

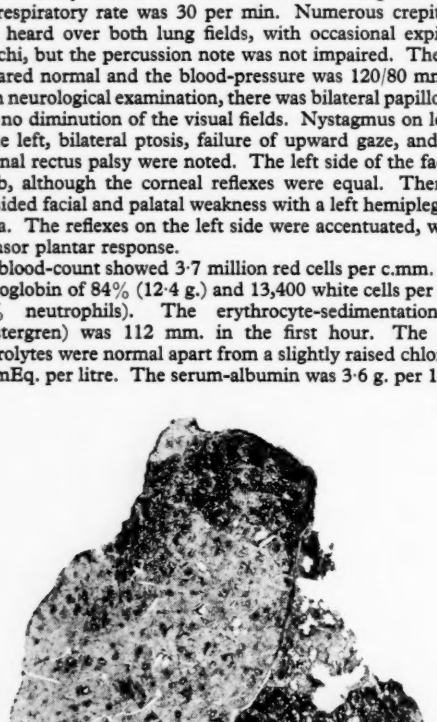

Fig. 2—Paper-mounted large section of left lung stained with hæmalum and Sudan IV showing diffuse infiltration of upper lobe and patchy involvement of lower lobe with lipid-containing "proteinosis" which stained a bright red. 2/5 Natural size. (Kindness of Prof. J. Gough.)

and the serum-globulin 3·0 g. Liver-function tests were normal. Lumbar puncture 2 weeks before admission had shown a pressure of 100 mm. cerebrospinal fluid. The C.S.F. was clear and sterile, and it contained 75 mg. protein per 100 ml., 80 mg. sugar per 100 ml., increased globulin, and 5 lymphocytes per c.mm. No malignant cells were seen in the mucopurulent sputum, which on culture yielded a mixed growth of commensals. X-ray of chest showed diffuse shadowing over both lung fields without enlargement of hilar glands or heart. Since the previous radiographs there had been some extension of the lesion in the right upper zone, while the left mid zone had a more nodular appearance. X-ray of skull showed no abnormality.

Treatment with large doses of penicillin and achromycin was begun. 2 weeks after admission he developed a painful swelling over the outer aspect of the right lower leg, over the site of a bruise which had been there since a fall about a month before. An X-ray of the leg showed a destructive lesion of the lower third of the shaft of the right fibula with considerable soft-tissue swelling adjacent to it. The appearances were very suggestive of an osteolytic secondary deposit, but aspiration of the swelling yielded pus and some blood, suggesting infection in an hæmatoma. The pus was sterile.

Despite further treatment with other antibiotics his condition deteriorated and he had a severe hæmoptysis. He died 4 days later, on April 25.

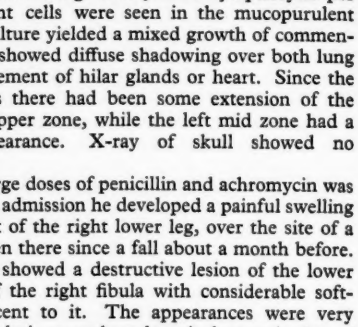

Fig. 3—Horizontal section of brain showing multiple metastatic abscesses mainly in occipital lobes at this level.

Postmortem Examination (38 hours after death).

The *lungs* (left 830 g.; right 940 g.) appeared voluminous and felt solid. They were deep red, without pleural thickening. On sectioning, it was seen that the alveolar pattern was preserved, but many alveoli had a solid yellow appearance because they were filled with a firm smooth infiltrate, of patchy distribution, most extensive in the upper lobes (fig. 1) and in the middle lobe on the right. Solid portions of lung sank in water. There was much pus in the bronchioles. The hilar lymph-nodes were not enlarged but were heavily impregnated with carbon.

Microscopically, scattered peribronchial alveoli—in all parts of the lung, but especially in the upper lobes—were filled with a finely granular, amorphous, lightly eosinophilic material similar to that seen in the original biopsy. The alveolar walls were thin and contained a few lymphocytes, but inflammatory reaction was absent. Large foamy macrophages were seen in several alveoli. Small acicular clefts, although sparse, were present in the alveolar material, which was slightly vacuolated in some places. Several more deeply staining aggregates, which appeared to be disintegrated cells (the so-called laminated bodies), were seen in the alveoli. The proteinaceous material filled many of the small bronchioles.

The histochemical reactions were similar to those already described, being positive with periodic-acid/Schiff stain, Sudan and oil red-O fat stains (fig. 2), Schultz method for cholesterol, and luxol-blue stain (suggesting the presence of phospholipid). The material stained metachromatic with 0·1% aqueous toluidine-blue at pH 4·3. It did not stain with thionin-blue but was weakly positive with alcian blue. Bacteria, fungi,

and *Pneumocystis carinii* were not seen. Negative reactions for iron, calcium, amyloid, and fibrin were obtained.

The *heart* showed an old healed pericarditis.

The *right leg* contained a chronic abscess in the soft tissue, associated with an osteomyelitis of the underlying lower third of the fibula. This bone was fractured, with a sequestrum between the two fragments at this level.

Fig. 4—Transverse section of pons showing multiple metastatic abscesses, one of which has ruptured into the floor of the fourth ventricle.

The *brain* (weight 1370 g.) was extremely swollen and contained numerous diffusely scattered small abscesses in both cerebral hemispheres and in the brainstem, more on the left than the right (figs. 3 and 4). A culture of the pus from these abscesses yielded proteus. Microscopically, the abscesses were surrounded by a well-developed capsule of purulent granulation tissue and appeared to be of similar age (about 3 months). The abscesses in the pons seemed to be more recent, without a well-defined capsule; and one had ruptured into the floor of the fourth ventricle terminally.

Discussion

Since this case was first reported by Hall (1960), many others have been described (Carabosi and Barta 1959, Edmondson and Gere 1960, Fraimow et al. 1960, Schoen et al. 1958, Sieracki et al. 1959, Slutzker et al. 1961, Snider et al. 1960, Taxay et al. 1960, Van Gool 1958). All these reports have confirmed the clinical, radiological, and histological features of the original case of Rosen et al. (1958) without contributing further information about the pathogenesis. They have, however, led to increased awareness of the condition so that an asymptomatic example was recognised by Furst et al. (1960) while Carlson and Mason (1960) diagnosed a case by examination of the sputum.

The course is variable and the condition has been studied by serial biopsy by Fraimow et al. (1960) over a period of $2^1/_2$ years during which time clinical, pathological, physiological, and radiological improvement took place. Of the twenty-seven cases reported by Rosen et al. (1958), thirteen remained stationary, four improved, and only one recovered. The only other reported recovery was that of a girl of 15 (Dick et al. 1957). The prognosis is therefore poor, and apart from the eight deaths in the series of twenty-seven collected by Rosen et al. (1958) there are at least eight other fatalities in the cases reported in the short period since their recognition.

There appear to be three main ways in which the disease proves fatal:

Obliteration of the respiratory surface leads to progressive pulmonary insufficiency, hastened at times by secondary infection. This seems to be the commonest cause of death, and occurred in five of the eight fatalities of Rosen et al., as well as in the cases reported by Levinson et al. (1958), Veterans Administration (1958), and Williams et al. (1960).

Cor pulmonale was responsible for the death of one of the cases of Rosen et al. (1958) and of cases reported by Payseur et al. (1958), Harrison et al. (1960) and Plenk et al. (1960).

Superimposed infection, due to bacteria or fungi, is the third cause of death. Nocardiosis is particularly liable to supervene in these cases and was found in cases 20 and 27 of Rosen et al. It was successfully treated in the cases of Burbank et al. (1960) and of Andersen et al. (1960), even though it had become disseminated in the latter. Other secondary invaders include cryptococcus (Rosen et al. 1958), candida (McDowell et al. 1959, Sieracki et al. 1959), and tubercle bacilli (Payseur et al. 1958).

Cerebral involvement has been described previously in only two cases, reported by Jones (1960). One of these developed cortical infarcts in the parietal lobes, due to plugging of vessels by hyphæ of mucormycosis, while the other had meningitis with a cerebellar abscess probably due to a proteus infection, since this organism had been cultured from the blood and urine during life. In this latter case severe inflammatory renal disease was found at necropsy, and this was a possible source of the proteus bacteræmia which caused or complicated the central-nervous-system lesions. (No cultures were taken at necropsy.) The present case seems to be the first with neurological complications due to multiple metastatic cerebral abscesses which had arisen from infection originating in the lungs.

It is of interest to consider the origin and contributory causes of these secondary infections.

Recurrent febrile episodes usually diagnosed and treated as "pneumonia" are described in most of the patients with pulmonary alveolar proteinosis and may initiate the disease. These cases seem to be unusually susceptible to pulmonary infection. The alveolar exudate may be patchy and can extend into the bronchioles, causing a partial or complete block. Secretions may thus be trapped and become infected, leading to systemic spread as in bronchiectasis.

Despite the reported improvement associated with adrenocortical steroid therapy (Moertel et al. 1959, Sieracki et al. 1959) such treatment may be dangerous in view of the liability of these patients to recurrent serious infections. It could not have contributed to the multiple widespread metastatic abscesses seen in the brain of our case, since treatment was stopped before the lung biopsy and about 10 months before the onset of neurological symptoms.

Summary

The terminal illness of a previously reported case of pulmonary alveolar proteinosis is described. The patient had neurological symptoms with signs indicating a brain-stem lesion.

Necropsy revealed multiple metastatic cerebral abscesses from which proteus was cultured. The organisms had come from a superimposed pulmonary infection. Such infection seems to be common in this disease.

Of the reported cases about a quarter had proved fatal at the time of the report. Only two with cerebral complications have been found.

Thanks are due to Dr. J. P. P. Bradshaw for allowing me full access to the clinical records and to Dr. G. F. M. Hall for the earlier details of the case and the original lung biopsy.

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A RELATIONSHIP BETWEEN INTESTINAL BACTERIA AND THE ABSORPTION OF VITAMIN B_{12} IN RATS WITH DIVERTICULA OF THE SMALL BOWEL

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PATIENTS with stasis of small-intestinal contents resulting from various abnormalities, such as diverticulosis of the small bowel, may have anæmia, impaired vitamin-B_{12} absorption, weight loss, and occasionally steatorrhœa. Intestinal bacteria have been implicated in this "blind-loop syndrome" because many of its manifestations are improved or corrected by giving antibiotics by mouth (Badenoch 1958). Certain features of the blind-loop syndrome have been produced in laboratory animals. The surgical formation of diverticula in the proximal and middle intestine resulted in severe morbidity and mortality in dogs (Tönnis and Brusis 1931) and rats (Watson et al. 1948). These animals developed macrocytic anæmia and steatorrhœa, and they lost weight (Watson and Witts 1952). In rats with intestinal diverticula the anæmia was corrected by folic acid, while chlortetracycline reduced the mortality (Watson and Witts 1952, Toon and Wangensteen 1950).

The present investigation was an attempt to study some of the quantitative relationships implied by the earlier observations of qualitative abnormalities. Although impaired absorption of vitamin B_{12} has often been reported in patients with the blind-loop syndrome, studies of intestinal vitamin-B_{12} absorption in animals with experimentally produced stasis of intestinal contents are lacking. In this study, the absorption of radiocobalt labelled vitamin B_{12} by rats with midgut diverticula was calculated from measurements of fæcal radioactivity after a dose of the vitamin by mouth. The theoretical justification for estimating vitamin-B_{12} absorption in this way has already been presented (Heinle et al. 1952, Moertel et al. 1959). We also measured the amount of indican in the urine of the rats because this is largely derived from the metabolic activity of intestinal bacteria (Dalgliesh 1955).

Methods

Female Sprague-Dawley rats (250 to 300 g.) were maintained in cages of 6 to 7 animals and fed a diet of 'Purina' chow. Two days before, and during, periods of study (which usually lasted one to three weeks) they were kept individually in metabolic cages, and given a fibre-free diet which was deficient in vitamin B_{12} and folic acid. This resulted in hard small fæcal droppings, and it therefore simplified fæcal collections. Urine and stools were collected separately.

1 ml. of 0·85% NaCl, containing 0·01 μg. of ^{58}Co-labelled vitamin B_{12} (specific activity=3 μC per μg.) which had been stored at −20°C, was given to each fasting unanæsthetised rat from a 1 ml. syringe through 10 cm. of polyethylene tubing which had been inserted through the mouth to the stomach. The radioactive vitamin which remained in the tubing was flushed into the stomach with 0·2 ml. of tap water from another 1 ml. syringe. A similar procedure was used to inject the labelled vitamin into 100 ml. volumetric flasks which were later used as "standards" for radioactivity determinations. The rats were deprived of food but not water overnight before intubation and for three hours afterwards. Both control and experimental rats were tested in each experiment.

Stools were collected for seven days, placed in 100-ml. volumetric flasks, and liquified by the addition of 15–20 ml. of a 1/1 mixture of concentrated nitric and sulphuric acids. An antifoaming agent* was added to prevent foaming. Sufficient tap water was added to the partially digested stools to bring them to volume. The flasks were then placed on top of a well-type scintillation counter, and counted to 1–2% accuracy. The radioactivity from the flasks was compared with that from the standards to determine the proportion of the dose of vitamin B_{12} which had been excreted in the stool.

Urine was collected daily during the test periods for at least three days, and stored at −4°C until analysed. The urinary excretion of indican was measured by the method of Meiklejohn and Cohen (1941). Urine-creatinine was estimated by the method of Bonsnes and Taussky (1945). The urine specimens from each of 5 unoperated rats and 5 rats with intestinal diverticula were separately subjected to paper-chromatographic analysis by the method of Dalgliesh (1955, 1956).

Diverticula of the small bowel were formed by transecting the small intestine 40 cm. from the ileocæcal valve. In the case of "self-filling" diverticula, the cut end of the distal intestine was anastomosed to the proximal intestine 8 cm. from the cut end of the cephalad segment. The cut end of the proximal segment was tied off with a purse-string suture. Thus the normal direction of peristalsis in the intestinal segment from which a diverticulum of this kind was made, would be towards the tied-off end. "Self-emptying" diverticula of the same length were prepared similarly, but their normal direction of peristalsis was towards the site of anastomosis (Cameron et al. 1949).

To eliminate intestinal bacteria, in some experiments rats were given neomycin for two days before and twenty hours after the fasting period in which the test dose of radioactive vitamin was given. The antibiotic was thoroughly mixed with the fibre-free diet. The amount of antibiotic ingested by each rat was calculated from the weight of residual food. When 9 unoperated rats were given neomycin in amounts of 100–300 mg. in each 15 g. of food, diarrhœa developed. After 25–50 mg. of neomycin per 15 g. of food, diarrhœa did not develop, and at this dosage the fæcal excretion of radioactive vitamin B_{12} was normal. Neomycin, therefore, was used at a concentration of 50 mg. in each 15 g. of food in experiments which will be described.

Results

After giving ^{58}Co-vitamin-B_{12} to 61 unoperated rats, 45·7±1·4 (S.E.)% of the radioactivity was recovered in the stools. Most of this radioactivity was excreted in the first three

* Antifoam A, from the Dow-Corning Corporation, Midland, Michigan.

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to four days after intubation. The calculated value for the proportion of labelled vitamin which had been absorbed was therefore 54·3% of the dose. Similar results have been reported by Watson and Florey (1955), Nieweg et al. (1956), and Taylor et al. (1958). In 21 rats, studied from four days to six months after the surgical formation of self-filling diverticula, the mean fæcal radioactivity was 81·6±2·5% of the administered dose. The intestinal absorption of labelled vitamin B_{12} was therefore 18·4% of the dose. The fæcal excretion was significantly ($P < 0.001$) greater than that observed in both the unoperated rats and in 8 rats with self-emptying diverticula, which had a mean fæcal excretion of 53·0±6·0% of the administered radioactivity (fig. 1). 9 rats which had normal values for fæcal radioactivity in the preoperative state, excreted high levels of radioactivity in the stools after the formation of self-filling diverticula. Repeated determinations of vitamin-B_{12} absorption in rats which were unoperated or had self-filling diverticula, gave similar values.

The daily excretion of indican and creatinine in the urine was determined in 35 unoperated rats, in 20 with self-filling diverticula, and in 8 with self-emptying pouches. The excretion of indican in unoperated rats was 1·4±0·1 (S.E.) mg. per 10 mg. of urinary creatinine. In rats with self-filling diverticula, however, the daily excretion of indican was 6·4±0·6 mg. —a value significantly ($P < 0.001$) greater than that observed in either the unoperated rats or in those with self-emptying diverticula, which excreted 2·6±0·4 mg. The increased amounts of indican in the urine of rats with self-filling diverticula were confirmed by paper-chromatographic studies.

Fig. 1 summarises the data on the urinary excretion of indican obtained when the absorption of radioactive vitamin B_{12} was tested. The values in 20 rats with self-filling diverticula were considerably higher than the corresponding values from 33 unoperated controls and from 8 rats with self-emptying diverticula.

The effect of neomycin on the absorption of labelled vitamin B_{12} and the urinary excretion of indican was assessed

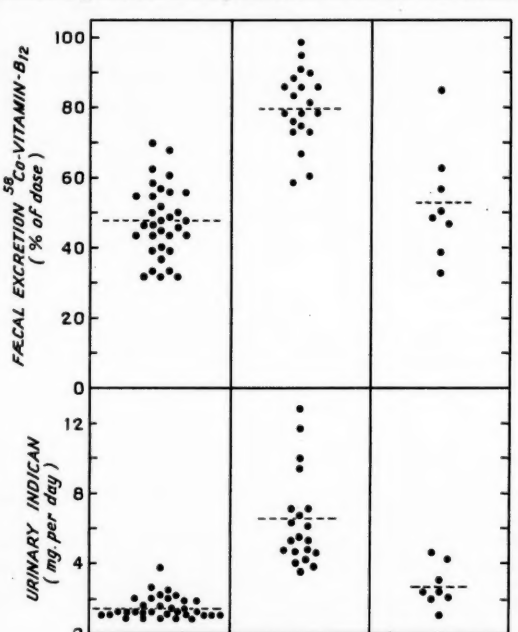

Fig. 1—The fæcal excretion of ^{58}Co-labelled vitamin B_{12} and the urinary excretion of indican, in rats with self-filling and self-emptying diverticula.

Individual values are represented by dots, mean values by lines.

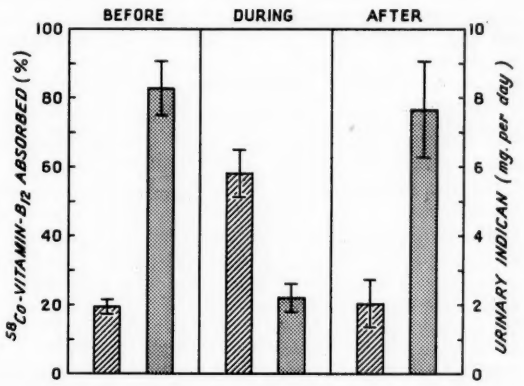

Fig. 2—The effect of neomycin on the absorption of ^{58}Co-labelled vitamin B_{12} (hatched), and the urinary excretion of indican (shaded) in 10 rats with self-filling diverticula during three successive seven-day periods.

The mean values are depicted by the heights of the bars, and the standard errors by the horizontal lines.

in 10 rats with self-filling diverticula and in 6 unoperated controls. The observations were made over three successive periods, and neomycin was given in the second period only. The mean weight of neomycin ingested daily by each rat during the antibiotic period was 45–65 mg. Feeding cups were thoroughly washed before the beginning of the third period. Neomycin administration was associated with a considerable decrease in fæcal radioactivity. The results of this experiment (fig. 2) show that neomycin produced a threefold increase in the mean proportion of labelled vitamin B_{12} which was absorbed by the rats during the second period. The mean absorption of the labelled vitamin in this period was 58% of the dose—a value very close to the mean absorption of vitamin B_{12} (54·3%) which was observed in the 61 unoperated rats. The excretion of indican in the second period by rats with self-filling sacs decreased to less than half the value observed in the first period when neomycin was not given. A return towards the previous abnormal values occurred in all 10 rats a week after the neomycin was stopped. The range of values observed was greater in this last period, possibly because the residual effects of the neomycin varied in the rats. 6 unoperated rats followed as controls through the three periods of study showed no significant alteration in their fæcal excretion of labelled vitamin B_{12}. Diarrhœa did not occur in either the experimental or control rats.

The mean survival-time of 9 rats with self-filling diverticula was only three months, while 7 rats with self-emptying sacs survived for seven and a half months after surgery. 5 of the latter rats lived until the end of all of the experiments, whereas none of the rats with self-filling sacs survived to this time. 5 of 10 rats with self-filling diverticula lost 57–97 g. in body-weight, 4 had no change in weight, and 1 gained 43 g. In contrast, 4 rats with self-emptying sacs gained 35–128 g. in body-weight.

At necropsy the self-filling diverticula were invariably enlarged and had thickened walls. Their lumens were filled with a foul grey semiliquid material containing loose hairs, hairballs, and grains of hard material. Mucosal ulcerations were not observed. In 6 rats the mean weight of the diverticula and their contents was 15·11 g.; the diverticula alone weighed 5·8 g., and therefore the mean weight of their contents was 9·3 g. The mean weight of the empty proximal gut was 3·7 g., and of the distal gut 3·2 g. The self-emptying diverticula, on the other hand, were not enlarged and were nearly empty, and their walls were about the thickness of normal intestine. In 6 rats these sacs had a mean weight of 0·7 g. both before and after removal of their contents. The proximal intestine weighed 5·0 g., while the intestinal segment

distal to the anastomosis weighed 3·4 g. The mean weight of the entire emptied intestine obtained from 4 unoperated rats was 6·1 g.

Discussion

Abnormal values for labelled-vitamin-B_{12} absorption and indican excretion in rats with self-filling diverticula are probably attributable to the metabolic activity of intestinal bacteria within the sacs, for the following reasons:

1. The large amounts of indican in the rats' urine (fig. 1) were presumably caused by increased activity of indole-producing bacteria, because indole formed by intestinal flora is generally accepted as the major source of urinary indican in the normal animal (Dalgliesh 1955). In these rats, increased urinary excretion of indican was always accompanied by impaired absorption of labelled vitamin B_{12}. This suggests that decreased absorption of the vitamin was also related to bacterial activity. On the other hand, in rats with self-emptying diverticula, the absorption of labelled vitamin B_{12}, and the excretion of indican, were similar to those in unoperated animals.

2. Values for the absorption of labelled vitamin B_{12}, and the urinary excretion of indican, in rats with self-filling diverticula quickly changed to normal after neomycin was given (fig. 2), and this is attributable to the antibacterial action of the drug. The neomycin experiments, therefore, lend further support to the view that the abnormalities of indican excretion and labelled-vitamin-B_{12} absorption in rats with self-filling sacs were the consequence of increased activity of intestinal bacteria. Furthermore, the intestinal flora probably grew again after neomycin was stopped, because the values for both indican and B_{12} became abnormal again during the third period (fig. 2), a little more than a week after neomycin was stopped. The experiments concerned with the excretion of indican in rats with self-filling diverticula support the previously cited work (Dalgliesh 1955) which shows that urinary indican is derived from the action of intestinal bacteria.

3. The large amounts of foul material within the self-filling diverticula give further evidence of increased activity of intestinal bacteria.

The data obtained by means of neomycin have several implications. Although a recent study suggests that neomycin may produce malabsorption in man (Jacobson et al. 1960), it is unlikely that it lessened the intestinal absorption of indolic substances in our experiments. The rats' excretion of indican was diminished when their intestinal absorption of B_{12} increased. Neomycin had no effect on the absorption of labelled vitamin B_{12} in unoperated rats. The decreased excretion of indican cannot be attributed to a lower intake of the precursors of indole, because the rats ingested the same mean weight of food whether or not neomycin was given.

The impaired absorption of labelled vitamin B_{12} in rats with self-filling diverticula may be attributable to loss of intestinal absorptive surface at a site which is crucial for vitamin-B_{12} absorption both in vivo (Booth et al. 1957) and in vitro (Strauss and Wilson 1958). But the return of labelled-vitamin-B_{12} absorption to normal after neomycin was given makes this possibility seem remote.

The activity of intestinal bacteria in the rats has been discussed in terms of measurements of the absorption of labelled vitamin B_{12}, and of the urinary excretion of indican. An exact analysis of the mechanisms by which intestinal flora affected these functions is not possible from the present data. Indican is largely derived from the degradation of tryptophan, or from the synthesis of indole by intestinal bacteria. Indole, which has been formed by bacteria from these substrates, may be absorbed by the intestine and subsequently converted to indican. It appears that this process was accentuated in the rats with self-filling diverticula. There are many possible ways (directly or indirectly) by which intestinal bacteria might have prevented the absorption of the labelled vitamin B_{12}; therefore it cannot be assumed that the vitamin was poorly absorbed because it too was utilised by the intestinal flora. The measurements of vitamin B_{12} absorption and indican excretion provided indices of the activity of intestinal bacteria in the rats in our experiments.

It seems likely that the bacteria in the lumens of self-filling diverticula needed extra nutrients for their increased activity and growth under conditions of " intestinal stasis ". Evidently the bacteria were able to " compete " successfully with nearby absorptive epithelial cells for these nutrients. If bacteria comprised a significant proportion of the 9·3 g. of material within the self-filling diverticula (as appears to be the case), then this flora may have utilised a relatively large part of the intraluminal nutrients during their logarithmic rate of growth. The metabolic fate of a variety of ingested foods and intestinal secretions may therefore have depended on the opposing actions of the bacteria and the intestines of their hosts. The extent to which this complex interaction results in inimical balances for the host remains to be determined. Clarification of this point may provide an explanation for the disease and death associated with self-filling diverticula.

Summary

The intestinal absorption of radioactive vitamin B_{12}, and the urinary excretion of indican, were measured in laboratory rats and in controls. The rats studied had " self-filling " diverticula of the small bowel—a condition causing localised intestinal stasis.

The absorption of the labelled vitamin was decreased and urinary indican was excreted in greater amounts by these rats as compared with the controls. These abnormalities were corrected by giving neomycin by mouth.

These experiments suggest that bacteria can survive within the alimentary tract, and greatly increase their activity in self-filling diverticula by the utilisation of various intraluminal nutrients—a situation which may be harmful to the host.

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SIGNIFICANCE OF NON-SPECIFIC GENITAL INFECTION IN UVEITIS AND ARTHRITIS

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Sir Benjamin Brodie's well-known description, in 1818, of 5 patients with arthritis, inflammation of the eyes, and urethritis was followed in 1836 by his account of a 6th case with a similar syndrome. 2 of Brodie's patients had iritis and in the other 4 cases the eye condition was described as conjunctivitis. Fournier (1868) studied 21 patients with "rhumatisme blennorrhagique": 10 of his patients had recurrent attacks of arthritis and 13 had involvement of the eyes. He was the first to describe the painful heel as part of the syndrome, "douleur exactement localisée sous un talon." Launois (1899), in a paper on "arthropathies recidivantes", described the relapsing course of the disease and discussed the development of uveitis in the later stages. He also gave the first clear description of the skin complication—"keratodermia blenorrhagica".

The triad of arthritis, genital infection, and inflammation of the eyes was, therefore, fully described by several authors before the end of the nineteenth century. They all emphasised that the arthritis usually involved the joints of the lower limbs, tended to run a relapsing course, and was often associated with uveitis.

Before the first world war the disease was ascribed to gonococcal infection. Indeed, Pierre Marie (1898) revised his ideas about the ætiology of spondylitis and attributed the majority of cases to gonorrhœa. Over the years, however, the view gained ground that many cases were not gonococcal. Fiessinger and Leroy (1916) in France, and Reiter (1916) in Germany, described the triad of urethritis, arthritis, and conjunctivitis following dysentery. King et al. (1946) described iritis as one of the complications of arthritis attributed to non-gonococcal urethritis. Harkness (1949) believed that in all his 126 cases of the triple syndrome the infection was non-gonococcal in origin, and both Harkness (1950) and Ford (1953) suggested that many conditions diagnosed as gonococcal arthritis were, in fact, associated non-specific infection which may have been the original cause of the arthritis.

Since Marie's statement attributing spondylitis to gonococcal infection of the genital tract, many authors have found an association between spondylitis and chronic genital infection.

Forestier (1935) described a series of patients in whom the two conditions were associated, and Volhard (1938) thought that the prostate gland was the main focus of infection in these cases. Romanus (1953) examined 117 cases of ankylosing spondylitis and found 91% of them to have chronic prostato-vesiculitis. He regarded the prostato-vesiculitis as non-specific and believed that chronic genital infection was the commonest cause of ankylosing spondylitis. Mason et al. (1958) confirmed Romanus' findings by examining 59 cases of ankylosing spondylitis and discovering chronic prostatitis in 83%.

The association of ankylosing spondylitis and uveitis is well known. Birkbeck et al. (1951) reported 11 cases in which iritis was the presenting manifestation of ankylosing spondylitis. Hart (1951) found that the incidence of uveitis in patients over 45 years of age whose disease was of 15 or more years' duration was slightly more than 40%.

The first large series of patients with uveitis to be carefully investigated for rheumatic diseases was that of Stanworth and Sharp (1956). They examined 209 patients and found an association between uveitis, Reiter's disease, ankylosing spondylitis, and other forms of spondylitis. The uveitis was almost entirely anterior in type and was non-granulomatous. Genital examination was not performed in this series.

Conjunctivitis is the commonest recorded ocular manifestation of Reiter's disease. Zewi (1947), however, found iritis in 1 out of 10 patients and Paronen (1948) in 6·6% of 334 patients with the dysenteric form of Reiter's disease. Ford (1953) reported recurrent iritis in 6 of 21 patients with chronic arthritis associated with urethritis of genital origin and Csonka (1958) recorded 21 cases of recurrent iritis in a similar group of 158 patients.

A careful survey of the literature revealed, therefore, not only that the cause of uveitis is often unknown, but also that the condition is often associated with Reiter's disease and ankylosing spondylitis. Reiter's disease is generally considered to be caused by non-specific genital infection, and ankylosing spondylitis is known to be associated with chronic prostato-vesiculitis. These associations suggested the idea of investigating a series of patients suffering from uveitis with special reference to the presence of genital infection. It was apparent from the literature that no such study had been previously undertaken.

Material and Methods

All the patients in this investigation were attending the Institute of Ophthalmology in London. All new patients with uveitis, whether anterior or posterior, were examined, thus eliminating the possibility of selection. A detailed clinical history was obtained and a thorough physical examination performed. Prostatic fluid was obtained by prostatic massage and five separate unstained specimens were examined microscopically at once. If no prostatic fluid was obtained on the first occasion the patient was requested to attend again for further prostatic massage. A gram-stained smear of the prostatic fluid was also examined. Culture plates for growing pleuropneumonia-like organisms and plates for aerobic and anaerobic cultures were inoculated with prostatic fluid. The centrifuged deposit of urine was inoculated on to culture medium for pleuropneumonia-like organisms and a stained smear of the deposit was examined microscopically. Detailed hæmatological studies including estimation of the hæmoglobin and erythrocyte-sedimentation rate, total red and white counts, and a differential white count were performed in all cases. Serological tests including a Wassermann and Kahn reaction, a complement-fixation test for toxoplasmosis, and a complement-fixation test for pleuropneumonia-like organisms were also carried out. The Rose-Waaler differential sheep-cell agglutination test was performed on a large sample of the patients. A Mantoux test, a dye test for toxoplasmosis, and urine analysis were also performed in all cases. Radiographs of the chest, sacroiliac joints, hands, feet, and ankles were taken in each case.

The uveitis was divided into anterior, posterior, and generalised. These subdivisions were based on the findings of the ophthalmologist who first examined the patients at the Institute and, in cases of doubt, were determined by further consultation with an ophthalmologist.

The prostatic fluid was considered to be abnormal if clumps of pus were found in the specimens or if more than ten leucocytes were present in several $^1/_{12}$-in. microscopic fields. These are the generally accepted

criteria for the diagnosis of chronic prostato-vesiculitis (Hinman 1935, Pelouze 1939). Repeated prostatic massage was required in several cases before an adequate specimen of prostatic fluid was obtained, some patients having to attend three or more times. The incidence of chronic prostato-vesiculitis may well be higher than the figures indicate because some patients could attend the Institute only once, and if an adequate specimen of fluid was not obtained they were excluded from the series.

The criteria for the diagnosis of ankylosing spondylitis are well known and have often been described in detail (Polley and Slocumb 1947, Mowbray et al. 1949, Hart et al. 1949, Hart 1955). A history of upward spread of the spinal involvement and of exacerbation of the symptoms following immobility was usually obtained. The movements of the lower spine and of the chest were often restricted. No case was diagnosed as ankylosing spondylitis in this series unless definite bilateral sacroiliac changes were present in the radiographs.

In this series the term Reiter's disease was used to describe a syndrome of uveitis or conjunctivitis, arthritis of a characteristic distribution and evolution, and evidence of genitourinary infection, often in the form of urethritis. There was no evidence to suggest that dysentery was a cause in any of the cases of Reiter's disease. A number of patients in the series presented with disease in which there was a history of acute genital infection some years previously, a history of subacute or chronic arthritis, and the finding of chronic prostatitis. These patients were considered to represent the chronic form of Reiter's disease and in some of them the acute phase of the genital infection had occurred in the past but had been unnoticed by them. The radiological changes of Reiter's disease have been thoroughly described by Murray et al. (1958) and Reynolds and Csonka (1958), and the criteria laid down by these authors were used throughout the series.

The term plantar fasciitis was used to describe a condition characterised by painful feet, usually with tenderness on the under surface of the heel and frequently associated with plantar spurs.

In a few cases it was extremely difficult to make the differential diagnosis between Reiter's disease, especially of the chronic type, and ankylosing spondylitis, and in some cases a history of past genital infection was obtained only at a second interview in which a more direct approach was used.

There was also a group of patients with radiological changes of sacroiliitis but no other abnormality in the X-rays. It is probable that these cases were examples of the early stage of the chronic type of Reiter's disease or, in some instances, early ankylosing spondylitis. As there was some doubt as to which group they belonged, it was considered advisable to classify them in a separate category as cases of atypical sacroiliitis.

No case of rheumatoid arthritis was seen, nor did this disease present any serious problems in differential diagnosis, except in one patient who had a positive differential sheep-cell agglutination test but typical X-ray changes of Reiter's disease and evidence of chronic genital infection.

Osteoarthritis occurred in some of the patients but was never the dominant clinical condition and did not present any special problems in diagnosis. Gout did not occur in any of the patients in the series.

Results

A total of 240 patients underwent these investigations, but complete assessment was possible only in 226; the remainder either failed to have one or more investigation performed or a specimen of prostatic fluid was not obtained.

Of these 226 cases, 4 had non-inflammatory lesions such as degenerative choroidal disease and none of these had prostatitis. 11 were diagnosed as Eales' disease (recurrent massive vitreous hæmorrhage) and only 1 of these was found to have chronic prostatitis. As these patients did not have true uveitis they have been excluded from the series.

Of the remaining 211 patients, 145 (68·7%) had evidence of chronic prostatitis by the criteria already defined. Anterior uveitis occurred in 152 cases (72%) and chronic prostatitis was found in 115 (75·6%). The uveitis was considered to be generalised in 29 cases (13·7%) and evidence of chronic prostatitis was found in 17 (58·6%) of these. Posterior uveitis was diagnosed in 30 cases (14·2%) and chronic prostatitis was found in 13 (43·3%). A small group of patients with heterochromic cyclitis numbering 12 was examined, and only 3 (25%) of these were found to have chronic prostatitis.

Chronic prostatitis was, therefore, a very common finding in patients with anterior uveitis. It was less common in those with generalised uveitis and uncommon in patients with posterior uveitis and heterochromic cyclitis, and its incidence in these cases was more comparable with that found in a series of controls.

The controls consisted of 75 patients of the same age-groups who were inpatients in the general medical and surgical wards of two large teaching hospitals and in whom the incidence of chronic prostatitis was estimated. 14 (18·6%) were found to have chronic prostatitis.

The anterior uveitis was acute in 133 cases (63%) and chronic in 19 (9%). Chronic prostatitis was much more common in the cases of acute anterior uveitis, where it was found in 107 (80·5%) and it occurred in only 8 cases (42%) of chronic anterior uveitis.

Reiter's disease was diagnosed in 45 cases (21·3%). 6 patients had active urethritis when they were first examined but only 1 of them had noticed this. Prostatitis was present in all 45 cases. The uveitis was anterior in 40 cases, generalised in 4, and posterior in 1. Recurrent attacks of uveitis had occurred in 16 cases.

Ankylosing spondylitis was found in 26 cases (12·3%). 25 of these patients had anterior uveitis, and prostatitis was present in all of them; 1 had acute generalised uveitis without evidence of active prostatitis. The uveitis was recurrent in 12 cases and the remaining 14 were suffering from first attacks.

Plantar fasciitis alone was found in 2 cases. Chronic prostatitis was present in both patients and the uveitis was anterior in type in both of them.

Atypical sacroiliitis and chronic prostatitis were found in 11 patients (5·2%). Acute anterior uveitis occurred in 6 of them, 2 had acute generalised uveitis, 1 chronic anterior uveitis, 1 acute posterior uveitis and 1 chronic posterior uveitis. Some or all of these patients were probably in the early stages of Reiter's disease or ankylosing spondylitis but it was impossible to make an accurate differential diagnosis.

The ages of the patients ranged from 18 to 75 years. Over half the patients were between 30 and 50, and radiological evidence of chronic Reiter's disease tended

to be more striking in the older age group than amongst the younger patients.

The Rose-Waaler differential sheep-cell agglutination test was performed on sera from 150 consecutive patients in the series. It was negative in 135 cases and positive in 15. A positive test occurred in only 3 patients with arthritis. Two of these had been diagnosed as cases of Reiter's disease and 1 of atypical sacroiliitis. There was no history of arthritis in their families, no clinical evidence suggestive of rheumatoid arthritis and the radiographs did not show changes typical of that disease. In none of the remaining 12 cases with positive agglutination tests was there any clinical or radiological evidence of rheumatoid arthritis.

Hæmatological investigations did not reveal any consistent abnormalities. The erythrocyte-sedimentation rate was raised in most cases of active ankylosing spondylitis and Reiter's disease, and in about a quarter of the cases of acute anterior uveitis with prostatitis only. Leucocytosis was uncommon.

Serological tests for syphilis were positive in 4 cases. In only 1 case was the uveitis probably due to syphilis. The other 3 cases had received adequate penicillin treatment in the past and the titre of their serological tests was low.

The gonococcal complement-fixation test was positive in 11% of the cases. This is a higher percentage of positive tests than would be expected amongst the general population, but the significance of a single positive test is difficult to evaluate.

Pleuropneumonia-like organisms were grown from the prostatic secretions in 23 cases (10·1%). These organisms were also found in the urine in 20 out of these 23 patients. This incidence is comparable with that found by Klieneberger-Nobel (1959) in a group of male patients attending the general medical outpatient department of the London Hospital. The complement-fixation test for pneumonia-like organisms was positive in 46 cases (20·4%). The incidence of positive complement-fixation tests in the general population is not yet known for certain. No correlation could be found between the positive tests and any of the categories of arthritis or fasciitis, or any of the types of uveitis.

Aerobic and anaerobic cultures of the prostatic fluid gave no positive information. Streptococci, staphylococci, and diphtheroids were grown in most cases and *Escherichia coli* in a few, but these organisms are usually regarded as contaminants of the male genitourinary tract.

Discussion

From this survey it is evident that chronic genital infection in the form of prostato-vesiculitis is often associated with anterior uveitis in male patients. No such association was demonstrated in cases of posterior uveitis or in heterochromic cyclitis in which the incidence of prostato-vesiculitis was much lower and approximated to that in a group of controls. Reiter's disease, which is known to be precipitated by genital infection, was a common finding amongst patients with anterior uveitis. Ankylosing spondylitis, which is usually accompanied by chronic prostato-vesiculitis, was also present in a significant proportion of cases. These findings suggest the possibility that the prostato-vesiculitis is the common factor between the uveitis and the arthritis. Reiter's disease and ankylosing spondylitis have many features in common and in some cases a differential diagnosis between them may be difficult or impossible. Atypical sacroiliitis and plantar fasciitis are also probably components of the same syndrome. It is tempting to consider these three types of arthritis and plantar fasciitis as manifestations of one disease which is caused by genital infection and of which anterior uveitis is a common component. Absolute proof of this hypothesis is lacking although the evidence points in that direction.

In this survey bacteriological and serological investigations failed to reveal a likely causative organism. No support was given to the suggestion that pleuropneumonia-like organisms are a possible cause of the condition, although positive complement-fixation tests for pleuropneumonia-like organisms were obtained in an unexpectedly high proportion of cases.

This work deals only with the association of uveitis, arthritis, and chronic genital infection in men. Acute anterior uveitis also affects women but is more common in men than women. Both ankylosing spondylitis and Reiter's disease are also more common in men than in women (Oates 1959).

An investigation into the relationship of uveitis, arthritis, and chronic genital infection in women is urgently required. The outstanding difficulty in such an investigation would be the assessment of the state of the genital tract for there is considerable variation of opinion about this matter and criteria for diagnosis in women are difficult to establish.

Progress in the diagnosis and treatment of this condition is hindered by the failure to find the causative organism of non-specific urethritis and chronic genital infection. Further research into this aspect of the problem is urgently required, using new and improved techniques.

Summary and Conclusions

211 male patients with uveitis have been fully investigated. Chronic genital infection in the form of prostato-vesiculitis was found in 145 (68·7%). Of 152 patients with anterior uveitis, chronic prostato-vesiculitis was present in 115 cases (75·6%). In a group of 75 controls chronic prostato-vesiculitis was present in 14 cases (18·6%).

Reiter's disease occurred in 45 cases (21·3%) and ankylosing spondylitis in 26 cases (12·3%). Atypical sacroiliitis and plantar fasciitis were found in a small number.

Extensive bacteriological and serological investigations failed to reveal a likely causative organism.

The association of chronic genital infection with anterior uveitis, Reiter's disease, ankylosing spondylitis, atypical sacroiliitis, and plantar fasciitis may constitute a single syndrome of which the most likely cause is the chronic genital infection.

I wish to thank Sir Stewart Duke-Elder and members of the staff of the Institute of Ophthalmology for their help and cooperation, Mrs. E. Klieneberger-Nobel for her work with the pleuropneumonia-like organisms, and Mr. S. Goldsmith for his invaluable nursing and technical help. Mr. Ambrose King gave encouragement and advice throughout the investigation, and I am very grateful to him. This work was performed while the author was in receipt of a grant-in-aid from the United States National Institutes of Health as a member of a group investigating non-specific urethritis under the direction of a working party of the Medical Research Council.

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CONGENITAL IODIDE GOITRE IN TWINS

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IODIDE goitre—the development of a goitre in a patient taking iodides but having no primary thyroid disorder—has been recognised only in recent years. About 30 cases are on record, most of them reported since 1945 (Morgans and Trotter 1953, 1959, Turner and Howard 1956, Paris et al. 1960, Burrows et al. 1960). Iodide goitres are apt to arise in asthmatics or patients with chronic respiratory disease who take iodides over long periods. It seems that only in a few such patients are iodides goitrogenic; Falliers (1960), for example, found goitres in only 2 of 101 asthmatic children taking potassium iodides under close medical supervision.

Morgans and Trotter (1959) reported 4 cases of goitre in patients taking 'Felsol' powders. They showed that iodopyrine, one of the ingredients of felsol, inhibited the organic binding power of the thyroid, and they suggested that this effect was due to the iodide liberated from iodopyrine in the gut. One of their cases was the baby of a mother who had chronic asthma and who developed a goitre associated with felsol therapy before and during pregnancy. At birth the baby had a large goitre which caused dyspnœa and cyanosis but which regressed without specific treatment.

The spontaneous regression of iodide goitres when the goitrogen is recognised and withdrawn makes surgery unnecessary and accordingly biopsy studies are uncommon. Recently we have had the opportunity of studying two infants (binovular twins) with congenital goitres whose mother had a goitre due to felsol. Both infants died, one at 11 hours and the other at 38 days.

Case-record

A woman of 40 was first admitted to the Princess Mary Maternity Hospital in May, 1959, because of pregnancy complicated by chronic bronchitis and severe œdema of the legs. She also had a large symmetrical goitre. Between 1939 and 1954, when the goitre was first noticed, she had 7 children, all born healthy and at term. About 1951 she began to take 3 to 5 felsol powders per day to help the chronic bronchitis. In 1957 investigations showed that, in addition to chronic bronchitis and bronchospasm, she had a smooth firm symmetrical enlargement of the thyroid, puffiness of the face and hands, coarse hair, and a husky voice. Although she looked hypothyroid the blood-cholesterol was 180 mg. per 100 ml. and the basal metabolic-rate was + 10. There was a rapid initial uptake of radioactive iodine but the peak uptake was within normal limits. Between May and September, 1959, she came into hospital three times during her eighth pregnancy with dyspnœa, leg œdema, and mild hydramnios. The goitre was still large, firm, smooth, and symmetrical. Her final admission was on Sept. 7 and twins were delivered on Sept. 16. Bilateral tubal ligation was performed 3 days later and she was discharged on Sept. 29. She took felsol throughout the pregnancy until admitted to hospital on Sept. 7 but not thereafter. During the 22 days in hospital her goitre became smaller.

At birth both twins had an obvious goitre, the glands being firm and symmetrically enlarged. The first twin, a boy of 3 lb. 14 oz. (1750 g.) made satisfactory progress and by two weeks of age his goitre was almost gone. At 34 days of age he weighed 5 lb. 10 oz. (2548 g.) and was discharged from hospital dying 4 days later from a fulminant gastroenteritis. The second twin, a girl of 4 lb. (1812 g.) died 11 hours after birth from hyaline membrane disease.

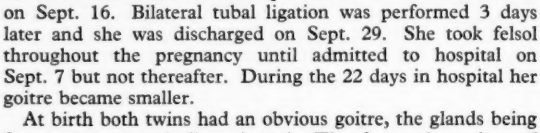

Fig. 1—Thyroid of twin dying at 11 hours, showing well-filled vesicles and prominent epithelium (×110).

Changes in the Thyroid

The thyroid of the second twin showed the most striking changes. The gland weighed 10 g. (average normal mean 1·4 g.) and was diffusely and symmetrically enlarged with several large surface veins. There was much variation in the size and shape of the vesicles and in their colloid (fig. 1). The colloid sometimes showed peripheral scalloping. Some vesicles, usually the smaller ones, were either empty or contained pale cells in various stages of preservation. These cells seemed to be detached thyroid epithelial cells which are commonly seen in newborn infants. The epithelium lining the vesicles was cuboidal, becoming columnar towards the periphery of the gland. Occasionally very large compact nuclei were seen. Papillary infoldings of the epithelium were infrequent but when seen were in the peripheral vesicles. The gland was not unduly vascular and there was no cellular infiltration or fibrosis.

The thyroid of the first twin, dying at 38 days, was slightly enlarged and weighed 7 g. (normal range 4–5 g.). Histologically the vesicles varied considerably in size and either contained no colloid or were incompletely filled by poorly staining colloid (fig. 2). The lining epithelium was cuboidal in type and there were very occasional epithelial infoldings. There was no excessive vascularity and no cellular infiltration or

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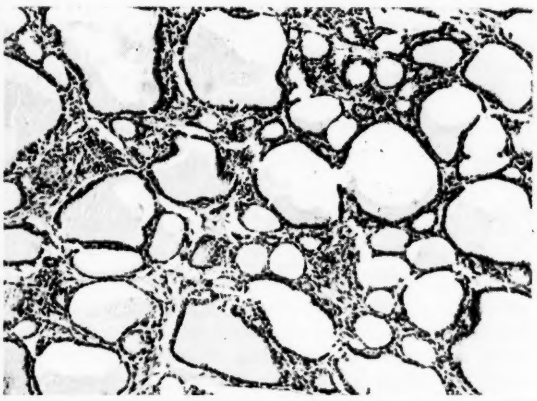

Fig. 2—Thyroid of twin dying at 38 days, showing poorly filled vesicles and flattened epithelium (×110).

fibrosis. The main differences from the second twin were the reduced colloid content, smaller vesicles, and the lower epithelium.

Discussion

Pathogenesis

It is generally held that high levels of plasma-iodides prevent the organic binding of iodine in the thyroid gland. The ultimate effect is lack of thyroxine and clinical hypothyroidism, and the goitre is thought to be caused by excessive thyroid stimulating hormone released by the pituitary.

When, as in the case of this mother, there is no primary maternal thyroid disease but a known goitrogen has caused a maternal and fœtal goitre, the pathogenesis of the fœtal goitre is more difficult to interpret. Normally the fœtal pituitary-thyroid axis appears to function independently. Maternal thyroxine is known to cross the placenta slowly (Hubble 1959) but in insufficient quantities to interfere with the fœtal thyroid. It is generally held that T.S.H. does not, in the normal pregnant woman, cross the placenta. Since iodides can cross the placenta freely it seems most likely that they directly caused the goitres in our cases. We suggest that in each case the organic binding power of the fœtal thyroid was blocked and that a goitre resulted from oversecretion of the T.S.H. from the fœtal pituitary. The possibility remains however that the maternal T.S.H., which might well be increased in this mother, could have crossed the placenta and stimulated the fœtal thyroids.

Histology

Iodide goitres have been described by some as colloid (Bell 1952, Morgans and Trotter 1953, Burrows et al. 1960) and by others as hyperplastic (Turner and Howard 1956, Paley et al. 1958, Paris et al. 1960). Burrows et al. (1960) point out that the histological appearance of the thyroids in these cases probably depends on whether the patients are taking iodides continuously up to the time of operation.

Petty and DiBenedetto (1957) reported an infant with a congenital iodide goitre which weighed 42 g. The mother had taken iodides for longstanding asthma throughout the pregnancy up to the delivery. The infant lived 30 minutes and the thyroid showed a colloid goitre with large vesicles lined by flattened inactive epithelium.

The appearances in the thyroid of our second twin, dying at 11 hours after birth, are regarded as abnormal, having the features of a colloid goitre but also showing some evidence of hyperplasia of the vesicular epithelium. It is possible that the withdrawal of the iodides for 9 days before delivery was sufficient to account for the epithelial hyperplasia in a goitre basically colloid in type. In the longer-lived twin iodides had been withdrawn for 47 days. The goitre disappeared and the size of the vesicles and their colloid content were reduced. We interpret our cases as supporting the contention of Burrows et al. (1960) that an iodide goitre is colloid in type. When the iodides are withdrawn, however, the initial histological response is one of epithelial hyperplasia. The crucial factor therefore in the histology of iodide goitre is the time interval since the last dose of iodide, or felsol powder, taken by the patient before operation.

Summary

Two cases of goitre are described in the binovular twins of a mother who for years had taken 'Felsol' powders for chronic bronchitis and bronchospasm. The pathogenesis and histology of these goitres are discussed.

We are indebted to Prof. J. K. Russell, Prof. S. D. M. Court, and Dr. C. E. Cooper for permission to publish these cases.

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Addendum

Since this paper was submitted Oppenheimer and McPherson (*Amer. J. Med.* 1961, **30,** 281) have published a case of iodide goitre and myxœdema, and they conclude that both depend on the length and regularity of iodide therapy or on a sensitivity to iodides possibly associated with some subtle thyroid defect.

SKELETAL INFECTION AS A COMPLICATION OF GENERAL SURGERY

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THIS paper describes acute osteomyelitis and septic arthritis complicating relatively clean general surgical operations. The occurrence of 8 such cases in one general hospital within three years suggests that the condition is more common than a total of 56 published cases would indicate. A disturbing feature of this complication is that it is often due to a penicillin-resistant *Staphylococcus aureus*.

Case-histories

Case 1.—Female, aged 72. Partial gastrectomy. Eight days after the operation she developed suppurative arthritis of the left knee due to a pneumococcus. Treatment with systemic and intra-articular penicillin resulted in complete recovery.

Case 2.—Male, aged 63. Suprapubic prostatectomy. Ten weeks after the initial operation a urethral dilatation was carried

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out; soon afterwards he developed suppurative arthritis of the left shoulder due to a penicillin-resistant staphylococcus. After a further four weeks he developed a similar arthritis in the other shoulder. These were treated with antibiotics and by aspiration; the left shoulder had to be incised. Finally, both joints recovered completely.

Twenty-two weeks after the initial operation, he had an osteomyelitis involving the fourth and fifth lumbar vertebræ. This settled with rest in bed and traction, followed by a posterior spinal support.

Case 3.—Male, aged 65. Suprapubic prostatectomy and vesical diverticulectomy. Twelve weeks later he developed an osteomyelitis involving the second and third lumbar vertebræ. This settled completely with antibiotics, rest in bed and traction, followed by a posterior spinal support.

Case 4.—Male, aged 40. Partial gastrectomy. After the operation he had an external duodenal fistula, and a pneumonia due to a penicillin-resistant staphylococcus. Seven weeks after the operation, there was a suppurative arthritis of the right knee due to a similar staphylococcus. This was controlled with systemic erythromycin and intra-articular chloramphenicol; but the patient died of multiple abscesses and cachexia.

Case 5.—Male, aged 66. Cystoscopy. A week later he developed osteomyelitis of the fifth and sixth cervical vertebræ. The condition was not immediately recognised and went on to subluxation. This was completely controlled by antibiotics, rest in bed and traction, followed by application of a leather collar.

Case 6.—Male, aged 61. Suprapubic prostatectomy. After the operation he had two attacks of retention requiring catheterisation. Twenty weeks later he developed an osteomyelitis involving the fourth, fifth, and sixth cervical vertebræ. This healed completely with antibiotics, rest in bed, and a leather collar.

Case 7.—Male, aged 43. Cystoscopy; retrograde pyelography for a calculous pyonephrosis. Four weeks later he had a suppurative arthritis of the left shoulder; aspiration yielded fluid containing numerous polymorphs but no organisms were isolated. The arthritis settled with aspiration and systemic antibiotics. It recurred after nephrectomy but again settled completely with antibiotics and aspiration.

Case 8.—Male, aged 70. Suprapubic prostatectomy. A week after the operation he developed a suppurative arthritis of knee, due to a penicillin-resistant staphylococcus. The condition of the joint did not settle with antibiotics, splintage, and aspiration; finally the joint was explored. The infection subsided but he was left with fibrous ankylosis.

Discussion

Primary Surgical Procedure

The operations most often followed by bone or joint infections are those on the genito-urinary system, particularly prostatectomy:

Prostatic Operations		Cystostomy	6
Suprapubic prostatectomy	21	Partial cystectomy	1
Transurethral prostatectomy	8	*Renal Operations*	
Prostatic massage	1	Pyelolithotomy	4
Drainage of prostatic abscess	1	Nephrectomy	3
Urethral Operations		Drainage of perinephric abscess	1
Dilatation	13	Uretero-enteric anastomosis	1
Vesical Operations		*Non-genito-urinary Operations*	6
Cystoscopy	5		

Manipulation and instrumentation of the genito-urinary organs in particular is frequently followed by a bacteræmia due to cocci as well as bacilli (Scott 1929, Barrington and Wright 1930, Hyman and Edelman 1932, Waisbren 1951).

Bacteriology

The organism most commonly isolated from the infected bone or joint was *Staph. aureus* (see table). In the urological cases this contrasts with the organisms—usually *Bacterium coli*, *Pseudomonas pyocyanea*, and *Proteus vulgaris*—obtained from culture of the urine. Blood-culture yielded staphylococci and bacilli with almost equal frequency. This discrepancy suggests that

BACTERIOLOGY

—	Bone and joint	Blood	Urine
Hæmolytic streptococcus	..	1	..
Non-hæmolytic streptococcus	..	1	3
Staphylococcus aureus	9	2	3
Coagulase-negative staphylococcus	..	1	..
Pneumococcus	1	..	..
Bacterium coli	..	1	14
Salmonella typhi	..	1	..
Bacterium aerogenes	1	1	6
Proteus vulgaris	..	2	9
Pseudomonas pyocyanea	4	1	10
Gram-positive bacillus	1	..	..

the infection of the catheter or operation site is a mixed one, and is followed by a bacteræmia also due to a mixture of organisms. However, the organism which survives and causes the lesions of the bones or joints is that which usually flourishes in and infects these sites—i.e., *Staph. aureus*. Thus, unless evidence to the contrary can be obtained by direct culture from the infected site, it must be assumed that the skeletal lesion is due to a "hospital" *Staph. aureus*, and antibiotics currently used for the treatment of such an infection should be administered.

Sites

Spinal column.—The most common site of bone or joint infection following general surgical operations was the spinal column, particularly the lumbar region:

Cervical spine (including 1 case with hemiparesis)	7	49
Thoracic spine (including 2 cases with paraplegia)	16	
Lumbar spine (including 2 cases with psoas abscess)	26	
Sacroiliac joint	1	23
Hip (symphysis pubis affected in 6 cases)	11	
Knee	3	
Tibia	2	
Sternoclavicular joint	1	
Shoulder	4	
Elbow	1	

This is a distribution similar to that of ordinary acute osteomyelitis in the adult (Wilensky 1929, Kulowski 1936, Turner 1938, Wear et al. 1952, Wiley and Trueta 1959). As a rule, two adjoining vertebræ were affected. On our radiographs the earliest destructive changes in the vertebral bodies appeared close to the intervertebral disc (see figure), thus confirming the recent work of Wiley and Trueta (1959) that vertebral osteomyelitis commences in the metaphyseal region of the vertebral body.

Case 2. Early osteomyelitis of the spine following prostatectomy.

Peripheral lesions. — Peripheral bones and joints were affected about half as often as the spinal column. Contrary to the opinion of Wiley and Trueta (1959), the evidence of the collected cases and our own experience prove that the peripheral lesion was more commonly a suppurative arthritis than an osteomyelitis.

Among the cases reviewed here, the hip was most frequently affected (10 patients, 11 hips). Most hips (7) seem to have become infected after an osteitis pubis, but in 4 cases the infection was primarily synovial.

In 9 patients, lesions had developed in peripheral sites other than the hip; all but 2 of these were cases of suppurative arthritis. 5 of the patients are reported by us; but Watkins et al. (1956) refer to several cases of peripheral suppurative arthritis following cystoscopy. This suggests that the condition is commoner than might be supposed from the small number of recorded cases.

Route of Infection

Clearly, the lesions of the peripheral bones and joints are due to an arterial spread of the bacteria. In our opinion, the vertebral osteomyelitis also is due to arterial spread, since the destruction of the vertebral bodies began in the metaphyseal region, which can be injected only through the spinal arteries and not through the paravertebral venous system (Wiley and Trueta 1959). Thus, we disagree with those authors (Batson 1940, 1957, Deming and Zaff 1943, Sherman and Schneider 1955, Lame 1956, Liming and Youngs 1956, Henriques 1958) who believe that the paravertebral system of veins is the principal channel through which infection reaches the vertebræ.

Clinical Features

The onset of the bone or joint infection was usually delayed until one to eight weeks after the primary operation:

Less than 1 week	2
1–4 weeks	30
4–8 weeks	10
8–16 weeks	6
Over 16 weeks	6

In about a third of the collected cases, this interval was completely uneventful; the rest of the patients had a mild pyrexia or other signs of infection.

The general symptoms due to the infective lesion were often mild, being less severe than those usually seen in primary osteomyelitis of the spine or in septic arthritis. In many cases, though not in all, the local signs were mild too; this often caused delay in establishing the diagnosis. The mildness of the symptoms contrasted with the destructive nature of the local lesion. The white-cell count did not help to establish the diagnosis, since it was seldom significantly increased. The erythrocyte-sedimentation rate, however, was usually raised.

Management

In addition to antibiotics, the patients with spinal osteomyelitis were treated by rest in bed and by traction followed by application of a posterior spinal support or a collar. Most cases healed with this conservative treatment and spontaneous ankylosis occurred in six to twelve months; there was little indication for posterior spinal fusion as advocated by Leigh et al. (1955).

Suppurative arthritis of the peripheral joints was usually treated by antibiotics and aspiration. Although many of the joints recovered with this conservative treatment, one of the knees reported by us and every one of the hips suffered considerable damage. This we attribute to the delay in effecting adequate drainage of these joints. In the infected hips, particularly, the results reported are so poor that, if the patient's general condition permits, early arthrotomy should be undertaken (Watkins et al. 1956).

Summary

1. 8 further cases of bone or joint infection secondary to genito-urinary or abdominal surgery are described, and the other 56 published cases of this condition are reviewed.

2. In many cases this infection is due to a penicillin-resistant *Staphylococcus aureus*.

3. It is suggested that not only the peripheral lesions but also vertebral osteomyelitis are due to invasion by organisms by the arterial route.

4. Since 5 of the new cases were suppurative arthritis, this condition appears to be commoner than is generally supposed. The importance of adequate drainage of the joints, particularly the hips, is emphasised.

Our thanks are due to Mr. W. M. Beattie, Mr. F. C. Dwyer, Mr. J. G. Gow, Mr. G. V. Osborne, Mr. J. M. Quinlan, and Mr. J. Cosbie Ross for permission to publish cases treated on their units.

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ANGIOGRAPHY IN ACUTE HEAD INJURIES

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CAROTID angiography was at first reserved for cases of presumed intracranial aneurysm, in which the immediate danger of the aneurysm outweighed the long-term hazards from radioactive 'Thorotrast'. Löhr (1936) first published his encouraging experience with 31 carotid angiographies in a five-year series of over 800 head injuries. When safer iodine compounds became available, others followed this lead.

The alternative method of investigation by multiple cranial burr-holes has remained in favour largely in this country (Lewin 1958, Hooper 1959, *Lancet* 1959). In contrast, neurosurgeons in Europe and the Transatlantic countries have employed angiography increasingly. Indeed, the burr-hole procedure has been dubbed the "woodpecker operation". Obviously burr-holes are suitable for disclosing effusions on the convexity of the brain; they contribute nothing but consternation when only a tense brain is revealed, caused perhaps by laceration, œdema, or a clot in an inaccessible site. They may also fail to reveal subfrontal or infratemporal clots.

In Bristol carotid angiography has long been favoured in the management of cases of acute head injury, and the method appears to be safe. Dr. J. L. G. Thomson, the

neuroradiologist in Bristol, and all of the neurosurgical team are now performing about 700 angiographies a year on all types of cases, mostly under local anæsthesia, and without notable incident. In this respect our experience differs from that of Rowbotham et al. (1953). It is true that when a patient is deteriorating clinically, worsening due to angiography may be concealed. However, Bull et al. (1960), investigating cases of "acute stroke", were able to say that in no case could permanent damage be unequivocally attributed to angiography. Wertheimer et al. (1956), reporting a series of 73 angiograms used in the management of head injuries, found no case adversely affected by the procedure. Engeset (1946, 1950), Kristiansen (1948), Carton (1954, 1959), Laine et al. (1955), Lofstrom et al. (1955), Fasiani (1956), Picot et al. (1957), Wertheimer et al. (1958), Pecker et al. (1959), and Ostrovskaia and Shimanko (1960) all support and illustrate the value of angiography in head injuries.

Laterally placed surface effusions have a characteristic appearance, demonstrated best in the venous phase of the angiogram. When they are situated anteriorly or posteriorly, oblique views may be required to complete the diagnosis. Petit-Dutaillis et al. (1956) discovered an extradural clot in the posterior fossa which was revealed by separation of the torcular Herophili from the inner table, and operated successfully. Extradural hæmatoma at the vertex has been similarly recognised by depression of the sagittal sinus (Wickbom 1949). The presence of an intracerebral hæmatoma may be inferred from the appearance of comparative avascularity in one region (Lafou et al. 1955, Irsigler 1958), or from the fact that shift of the anterior cerebral artery is greater in amount than would be caused by the surface collection which is quite often simultaneously demonstrated. Sedzimir (1955) has drawn attention to traumatic occlusion of the intracranial carotid artery.

Campbell and Campbell (1961) show how an interhemispheric clot may be recognised by an avascular zone seen between the falx and the medial surface of the brain, and by separation of the callosomarginal from the pericallosal artery, in the anteroposterior view.

Successive arteriograms at intervals may show reassuringly that traumatic or anoxic swelling of a lobe or hemisphere is subsiding (Pouyanne et al. 1956).

Many cases present soon after injury with syndromes causing some anxiety—e.g., a lucid interval, fluctuation of consciousness, or epilepsy with hemiparesis in sequence. The demonstration of a normal arterial tree is of the greatest help to the clinician.

The anterior cerebral artery may remain in the midline when there is a bilateral lesion. In 8 cases in the present series an acute subdural hæmatoma has been found on the side opposite to an extradural hæmatoma, and in 2 of them the anterior cerebral artery was not deviated. This emphasises the value of a bilateral examination, which may be achieved in some cases by compressing the opposite carotid artery during the injection of the opaque medium. Temporal lobe swellings of important degree may also cause little displacement of the anterior cerebral artery.

The Survey

A total of 620 cases over the ten-year period 1949–58 was analysed. In the earlier years facilities for angiography were limited, and the survey is therefore not of a homogeneous series. Nearly all the patients were admitted to the South Western Region Neurosurgical Department after consultation, and are consequently a selected group; the criterion for acceptance being that observation, special investigation, or operation might be required.

EXTRADURAL HÆMATOMATA

Of the 114 cases in this group, angiography was carried out in 34, and localised the effusion exactly. In 62 cases clinical evidence was sufficient to allow correct planning of the primary surgical treatment. In 24 others immediate operation on clinical grounds was indicated; 9 of these patients died.

In 4 patients without angiography, significant and fatal accumulations were found at necropsy.

There were 6 patients in whom the clot would not have been detected by conventional burr-hole technique; 5 had clots on the floor of the middle fossa, and these were revealed by angiography in 4 cases, and by craniotomy in the 5th. The 6th patient's frontal hæmorrhage was located by angiography after burr-hole exploration had revealed nothing but raised intracranial pressure. All 6 recovered.

In 14 cases the clinical and radiological findings were misleading, or inadequate for a clinical diagnosis. In 10 of these angiography revealed the site of the clot. Of the remainder, 1 was of the dangerous type to which Connolly (1956) has drawn attention, where operation was undertaken to close a fistula into the middle ear, and the hæmatoma was an unexpected finding; in the other 3 the hæmorrhage was found by operating. None of these 14 patients died.

In the whole group 30 patients died, and only 6 of these received angiography—the mortality-rate was 26%.

ACUTE SUBDURAL HÆMATOMATA

For the purposes of this paper, subdural hæmatomata were classified as acute if they were admitted within a week of injury. In borderline cases it must obviously be a matter of opinion whether the collection at the surface of the brain has contributed significantly to the syndrome, but fortunately this problem arose in only a small minority. Patients with small thin effusions were not included in this group of acute subdural hæmatomata.

In 5 cases an unsuspected and important subdural clot was found after death. In none of these had angiography been used to assist in diagnosis.

In 1 case with recovery a normal angiogram belied the presence of thin but extensive bifrontal collections, which were however revealed by operation. These would probably have been detected by oblique views.

10 patients had equivocal or misleading clinical signs, and angiography led to the correct diagnosis in all of them, 3 of them dying from their brain injury.

The last group are the temporal-lobe swellings accompanied by subdural hæmorrhage, of which there were 17, 12 having angiography. In all these the middle cerebral group of arteries was elevated; in 6 this was due to small intratemporal clot with local œdema; in 4 to contusion, laceration, or both. In 2 the cause was not found, because the patients improved without further operation. Without arteriography four clots were revealed at craniotomy; the fifth was "missed" and has already been referred to in the group of five unsuspected clots mentioned above. Lofstrom et al. (1955) have remarked that in the presence of temporal-lobe swelling shift of the anterior cerebral artery may be slight or non-existent, again drawing attention to the value of display of the cerebral vessels on both sides. All the intracerebral hæmatomata in this group were small, and these cases were therefore not included in the following group of intracerebral hæmatomata.

The mortality was 55% (51 deaths in a total of 92 cases).

INTRACEREBRAL HÆMATOMATA

This is probably the most important group in demonstrating the value of angiography.

There was a total of 25 patients, of whom 13 died (52%).

Of the 9 patients who had no angiogram, or angiography on the wrong side (2 cases), 6 died because the hæmorrhage was not diagnosed. 2 of them stopped breathing during anæsthesia, and the 3rd died suddenly, having been in good condition for the previous twenty-four hours.

The other 3 deaths were in patients whose hæmatomata were found at operation but who also suffered from cerebral œdema. 3 patients without angiography had their hæmatomata successfully removed at operation.

Arteriography was performed in 13 other cases, and in these the outcome was fatal only in 3. One of these patients, known to be a " bleeder " and to have recurrent intracerebral hæmatomata, could not be saved despite repeated exploration; he had what was later described as " Christmas disease ". The 2 others who died were suffering from cerebral contusion in addition. 12 of these angiograms localised the site of the hæmorrhage exactly; 5 were temporal, 5 frontal, and 2 parietal; 9 of the patients recovered. The 13th angiogram detected the side of the hæmatoma, though it was made on the side opposite to it, and craniotomy revealed the clot—this patient died with brain-stem hæmorrhages.

Most of the patients in this group were thought not to require immediate operation; 1 was considered too ill to be operated upon—1 of the 6 of the " missed " group of clots.

MISCELLANEOUS HEAD INJURIES

Normal Angiograms

Angiography was normal in 60 patients who were transferred to the unit because of a history or signs of possible neurosurgical significance. 7 of them were operated upon (6 burr-hole explorations and 1 craniotomy), which confirmed that no lesion requiring surgical relief was present. 7 also of this group died, no intracranial clot being found at necropsy.

It is therefore reasonable to infer that a normal carotid angiogram provides reliable evidence that in such cases as these operation is not required, provided there is no clincial evidence of intracranial hypertension.

Abnormal Angiograms

There were 20 cases showing displacement of the anterior cerebral artery, and operation was performed in 16, the lesions being either contusion or laceration of the brain, in some cases associated with thin subdural collections. 4 had displacement of 6 mm. or under, and recovered without operation. Oblique views were helpful in making the diagnosis certain in 3 of these cases, where routine views failed to demonstrate a collection at the surface of the brain. Slight shift of the anterior cerebral artery—6 mm. or less—may be inconsequential. However these cases must be observed carefully, and if clinical deterioration occurs, angiography should be repeated or ventriculography performed. 5 of these 20 patients died.

Hydrocephalus was demonstrated in 3 cases (wideswept pericallosal artery): 1 died with meningitis, 1 went on to an organic dementia and death, and 1 is in good health. In neither of the 2 who died was an intracranial hæmorrhage found at post mortem.

3 cases also had occlusion of the intracerebral carotid artery and none required operation. 2 of them died.

Discussion

Of the 620 cases surveyed, 174 had successful angiograms (28%). Angiography was materially helpful in the management of 15 of the 38 examined in the group of extradural hæmatomata, 86 of the 93 in the miscellaneous group, 20 of the 38 in the subdural hæmatomata, and 12 of the 17 in the intracerebral clots. Thus it was definitely useful in 69% of all cases.

The cases of " missed clots " produce most significant figures, since 13 out of the 15 patients had no angiography. The 2 who did have the examination were injected on the wrong side.

Inevitably a number of what eventually prove to be unnecessary examinations will be made—the normal angiograms in the miscellaneous group, for example. But at the time of admission the surgeon does not know that he has not a surgical problem on his hands, and a normal film is of great help in planning treatment which avoids operating.

It would be unwise to be carried away by uncritical enthusiasm for angiography without the application of clinical judgment—the most essential factor in the management of the complications of head injuries. Seriously ill patients may require immediate operation; should they remain unimproved after a surgical procedure is completed, angiography is well worth considering as an urgent measure (Whittaker 1960).

There are growing signs of approval of this valuable examination (Gibbs 1960, McKissock et al. 1960, *Lancet* 1960), culminating in the statement recently that " angiography is essential to the diagnosis of severe brain injury " (*Lancet* 1961).

It may be argued that it introduces dangerous delay in operative treatment, and this may well be so when films are not readily obtainable. This paper sets forth the experience in a unit where such difficulties have been overcome by the good will and foresight of the radiological staff.

Summary

A ten-year survey of cases of acute head injury treated in the South Western Regional Neurosurgical Unit shows that angiography is a most helpful investigation, and implies that some patients may be lost for lack of its use. It seems to be superior to that of multiple burr-hole exploration.

I am very grateful to the consultants in the Bristol Neurosurgical Unit for their help in this survey. My thanks are also due to Dr. J. L. G. Thomson, to Dr. L. Epszteyn for translations, and the staff of the medical library of Bristol University, without whose help this paper would never have been completed.

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Preliminary Communications

IMMUNOLOGICAL FUNCTION OF THE THYMUS

IT has been suggested that the thymus does not participate in immune reactions. This is because antibody formation has not been demonstrated in the normal thymus,[1] and because, even after intense antigenic stimulation plasma cells (the morphological expression of active antibody formation) and germinal centres have not been described in that organ.[2] Furthermore, thymectomy in the adult animal has had little or no significant effect on antibody production.[3]

On the other hand, there are certain clinical and experimental observations in man and other animals which suggest that the thymus may somehow be concerned in the control of immune responses. Thus, in acute infections, when presumably the need for antibody production is great, the thymus undergoes rapid involution; in patients with acquired agammaglobulinæmia the simultaneous occurrence of benign thymomas has been described,[4] and in fœtal or newborn animals, at a time when responsiveness to antigenic stimulation is deficient, the thymus is a very prominent organ.

The apparent contradiction between these two sets of observations may be partly explained by recent work,[5 6] which suggests that the thymus does not respond to circulating antigens because these cannot reach it owing to the existence of a barrier between the normal gland and the blood-stream. If the barrier is broken, for instance by local trauma, the histological reactions of antibody formation take place in the thymus.

In this laboratory, we have been interested in the role of the thymus in leukæmogenesis.[7] During this work it has become increasingly evident that the thymus at an early stage in life plays a very important part in the development of immunological response.

METHODS AND RESULTS

In the preliminary experiments mice of the C3H and Ak strains and of a cross between T_6 and Ak were used. The thymus was removed 1–16 hours after birth. Alternate littermates were used as sham-thymectomised controls—i.e., they underwent the full operative procedure, including excision of part of the sternum, but their thymuses were left intact. Mice in another group had thymectomy at 5 days of age. Wounds were closed with a continuous black silk suture and the baby mice were returned immediately to their mothers. No antibiotics were administered at any time either to the operated mice or to their mothers.

Mortality during and immediately after the operation ranged between 5 and 15% (excluding deaths due either to neglectful mothers or to cannibalism). Mortality in the thymectomised group was, however, higher between the 1st and 3rd month of life and was attributable mostly to common laboratory infections. This suggested that neonatally thymectomised mice were more susceptible to such infections than even sham-thymectomised littermate controls. When thymectomised and control groups were isolated from other experimental mice and kept under nearly pathogen-free conditions, the mortality in the thymectomised group was significantly reduced.

Absolute and differential white-cell counts were performed on tail blood at various intervals after thymectomy. The significant results of these estimations are summarised in fig. 1. In sham-thymectomised animals the lymphocyte/polymorph ratio rose progressively in the first 8 days of life to reach the normal adult ratio of $2{\cdot}5 \pm 0{\cdot}08$. In the animals whose thymus was removed on the 1st day of life the ratio did not increase significantly and was only $1{\cdot}0 \pm 0{\cdot}10$ at 6 weeks of age.

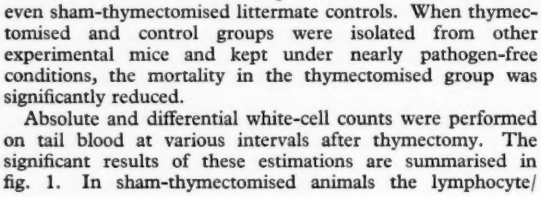

Fig. 1—Average lymphocyte: polymorph ratio of mice thymectomised in the neonatal period compared with sham-thymectomised controls. Statistical differences indicated.
o——o thymectomised mice.
●——● sham-thymectomised mice.

Histological examination of lymph-nodes and spleens of thymectomised animals at 6 weeks of age revealed a conspicuous deficiency of germinal centres and only few plasma cells (figs. 2 and 3).

At 6 weeks of age, groups of thymectomised, sham-thymectomised, and entirely normal mice were subjected to skin grafting, Ak mice receiving C3H grafts and vice versa, and $(AkXT_6)F_1$ mice receiving C3H grafts. The median survival time of skin grafts in intact mice, sham-thymectomised mice, and mice thymectomised at 5 days of age ranged from 10 to 12 days. In more than 70% of mice whose thymus was removed on the 1st day of life the grafts were established and grew luxuriant crops of hair. Most of these grafts were tolerated for periods ranging from 6 weeks to 2 months and

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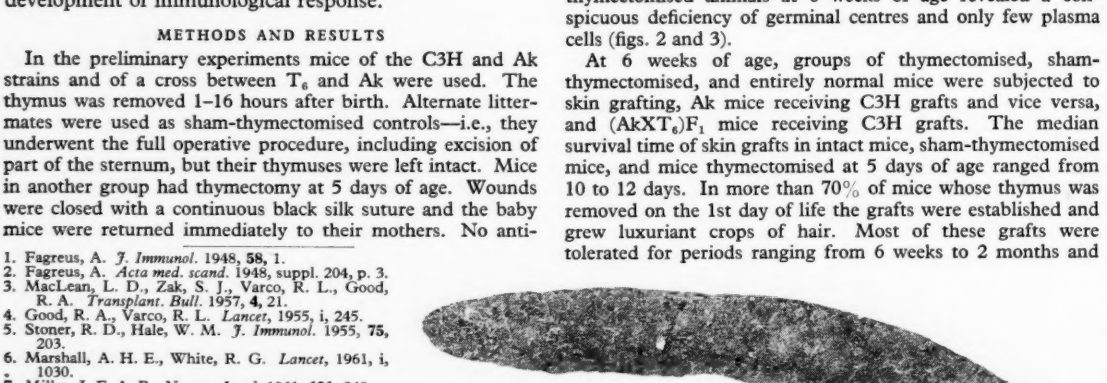

Fig. 2—Spleen of 6-week-old C3H mouse thymectomised at birth (× 20).

Fig. 3—Spleen of 6-week-old C3H mouse sham-thymectomised at birth (× 20).

SURVIVAL OF ALLOGENIC SKIN GRAFTS IN MICE THYMECTOMISED IN THE NEONATAL PERIOD

Group	Age at operation	Strain of mice	Skin graft	Number grafted	Number tolerant	Median survival time of graft (days)
Thymectomised	1–16 hours	C3H	Ak	7	5	45–101*
		Ak	C3H	6	4	41–90 *
		(AkXT6)F$_1$	C3H	8	8	50–118*
Thymectomised	5 days	C3H	Ak	5	0	11±0·7
Thymectomised and thymus-grafted 3 weeks later	5 hours	C3H	Ak	5	0	11–15
Sham-thymectomised	1–16 hours	C3H	Ak	6	0	11±0·6
		Ak	C3H	3	0	10±0·8
Intact		C3H	Ak	61	0	11±0·6
		Ak	C3H	45	0	10±0·9
		(AkXT6)F$_1$	C3H	10	0	11±0·1

* These figures apply to the tolerant mice.

some for even longer than 2 months. Thereafter they gradually diminished in size, lost their hair, and eventually disappeared. A small group of C3H mice thymectomised immediately after birth, which were 3 weeks later grafted with thymuses taken from C3H fœtuses towards the end of the gestation period, did not tolerate Ak skin grafts for more than 15 days (see table).

DISCUSSION

The above results indicate that thymectomy in the immediate neonatal period is associated with severe depletion in the lymphocyte population and serious immunological defects in the mature animal. Several hypotheses might account for these results. One is that the thymus, particularly in early life, regulates lymphocyte production, not only by being the main producer of such cells, but also by secreting a factor, such as Metcalf's lymphocytosis-stimulating factor,[8] which, after birth, stimulates lymphopoiesis in other lymphoid organs. In mice thymectomised at birth, the deficiency of lymphocytes would simply weaken the host's immunological defence as a whole. Another hypothesis attributes to the thymus a more direct role in the development of immunological response. During embryogenesis the thymus would produce the originators of immunologically competent cells many of which would have migrated to other sites at about the time of birth. This would suggest that lymphocytes leaving the thymus are specially selected cells, and this might possibly be correlated with their epithelial (rather than mesenchymal) origin[9] during embryogenesis. In accordance with elective theories of antibody formation,[10 11] genetically distinct clones of cells might differentiate at various stages during thymic morphogenesis. In parallel with experience gained from experiments on classical immunological tolerance,[12] one might predict that the originators of those cells capable of reacting with the more distantly related antigens would differentiate earlier in embryonic life than the originators of those cells concerned with more closely related antigens.

If this hypothesis is to be tested experimentally, there are obvious technical difficulties to be surmounted. It has been possible, however, to thymectomise and keep alive mice born by cæsarean section 1 day before the end of the normal gestation period. Even within this short period one might be able to obtain sufficient data to correlate the degree of tolerance of skin grafts of increasingly greater "foreignness" with the time at which thymectomy was performed.

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RELATIONSHIP OF DISTURBED PANCREATIC FUNCTION TO HÆMOSIDEROSIS

IT is well recognised that, whereas patients with idiopathic steatorrhœa absorb iron poorly and often have iron-deficiency anæmia, those with pancreatic steatorrhœa rarely become anæmic.

Closely related to this clinical finding is the observation made in cats by Taylor et al.[1 2] that ligation of the pancreatic duct is followed by intensive deposition of iron throughout the body tissues, the liver in particular being "packed with golden-brown hæmosiderin granules". Kinney et al.[3] demonstrated the same effect in dogs, and similar results were obtained in rats and mice [4] using *d, l*-ethionine to destroy the exocrine cells of the pancreas. Thus, in a variety of animals absorption of iron increases after destruction of the pancreas.

My studies of iron absorption in patients with chronic pancreatitis and pancreatic calcification, using a standard meal labelled with ^{59}Fe, have shown a similar increase in man (see table). Confirmation was obtained by examining

INCREASED IRON ABSORPTION AND UTILISATION IN UNTREATED PATIENTS WITH CHRONIC PANCREATITIS AND PANCREATIC CALCIFICATION

Sex	Hæmoglobin	Radioactive iron		
		Excreted in fæces (%)	Absorbed (%)	In blood (%)
M	14·0	76	24	0·5
F	14·5	75	25	1·0
M	13·1	69	31	0·5
*F	14·6	77	23	15·0
F	13·0	76	24	0·5
M	14·5	61	39	1·0

*Patient had a melæna one year previously.
Normal subjects absorbed 6%, with a range of 0–13%.

the liver of the 4 patients with calcification of the pancreas who have died in the Radcliffe Infirmary in the past ten years. In three, granules giving the characteristic reaction for iron (ferrocyanide-hydrochloride reagent) were found in large amounts equally in the hepatic parenchymal cells and in the Kupffer cells. In the fourth, in whom no iron was found in the liver, there was a history of repeated hæmorrhage from a duodenal ulcer.

My results confirm that, in man as in animals, iron absorption is enhanced by pancreatic damage; and a study of the literature suggests that absorption of iron may increase whenever the pancreas is severely damaged, and that pancreatic failure may be the prime cause of hæmosiderosis in man.

Andersen in 1938, in a review [5] of fibrocystic disease of the pancreas, commented on the rarity of anæmia and a

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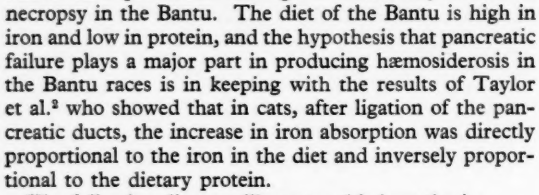
study of the case-reports of her patients shows that in 13 infants who died between the ages of one week and six months no fewer than 11 had hæmosiderosis of the liver and spleen.

Increased deposition of iron in the tissues is a salient part of the clinical picture of hæmochromatosis; but perhaps here also the damage to the pancreas is primary, because Sheldon [6] showed that severe pancreatic fibrosis occurs in 90% of cases and that some degree of pancreatic fibrosis is invariable.

Finally, the hæmosiderosis of the Bantu could be due to pancreatic failure, for the pancreas is one of the first organs to be affected by malnutrition and especially by deprivation of protein. Gillman and Gillman [7] have stated that pancreatic damage is commonly found at necropsy in the Bantu. The diet of the Bantu is high in iron and low in protein, and the hypothesis that pancreatic failure plays a major part in producing hæmosiderosis in the Bantu races is in keeping with the results of Taylor et al.[2] who showed that in cats, after ligation of the pancreatic ducts, the increase in iron absorption was directly proportional to the iron in the diet and inversely proportional to the dietary protein.

The following diagram illustrates this hypothesis:



The mechanism of this ability to absorb increased amounts of iron in states of disturbed pancreatic function is at the moment uncertain. Kinney et al.[3] noted that in dogs the increased absorption of iron which followed ligation of the pancreatic ducts was inhibited by feeding raw pancreas. In one of my patients with calcification of the pancreas in whom the iron absorption was studied before and after treatment with pancreatin granules, the treatment greatly reduced the amount of iron absorbed.

It seems, therefore, that there may well be a factor in the exocrine secretions of the pancreas which either directly or indirectly influences the absorption of iron. This possibility is receiving further study.

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ULTRASONICS IN RENAL BIOPSY

AN AID TO DETERMINATION OF KIDNEY POSITION

ULTRASONIC methods have been described for the detection of intra-abdominal masses, breast tumours, retinal tumours, intracranial lesions, and stones in the common bileduct at laparotomy.[8–14] As an aid to renal biopsy I have used a *simple unmodified* ultrasonic flaw-detector* to detect the depth and position of the kidney. It is particularly useful in those uræmic patients in whom intravenous pyelography cannot be carried out and plain X-ray of the abdomen does not clearly demarcate the renal outlines.

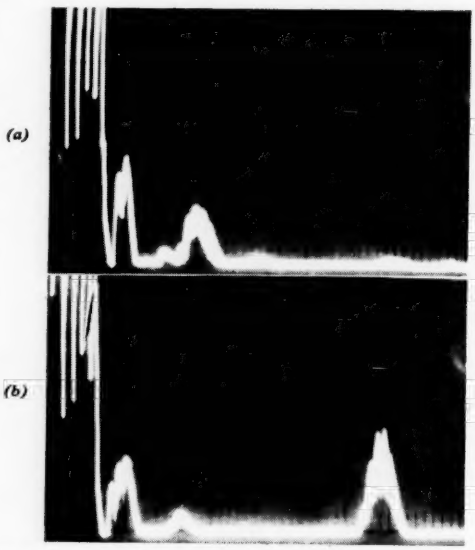

Fig. 1—Photographs of cathode-ray oscilloscope tube. (*a*) upper photograph taken in expiration; (*b*) lower photograph taken in inspiration.

Note the large deflection due to kidney at extreme right of (b), during inspiration, not present in expiration. Kidney depth 4·0 cm., confirmed by direct measurement. Deflections in (a) and (b) on the left are due to the probe and superficial tissues.

Principle.—Pulses of ultrasonic waves are produced by a quartz crystal coupled to a transmitter; the sound waves are reflected from the fat-kidney interface and are converted by the probe (which rests on the skin) into electrical energy which is amplified and shown as a deflection from the horizontal base line on a cathode-ray oscilloscope (C.R.O.), the horizontal distance of the deflection from the origin being related to the distance between kidney and quartz probe. Preliminary cadaver work had established a calibration curve relating depth of tissue in centimetres to arbitrary units of calibration on the C.R.O. scale.

The method of ultrasonic detection of kidney position and depth is as follows:

A 2·0 megacycles-per-second probe, 1 cm. in diameter, is applied to the skin over the renal angle, close contact being maintained by 'Polycell' or glycerine. The patient is asked to breathe deeply, and the probe is moved caudad until a deflection is seen on inspiration which is absent on expiration (see figure). The probe position is noted and this is taken to correspond to the position of the lower pole of the kidney on inspiration. The horizontal distance of the deflection from the origin is read off and converted to centimetres by reference to the calibration curve; the figure so obtained represents depth of the posterior surface of the kidney from the skin.

INVESTIGATION AND RESULTS

In 20 patients, (6 of whom were uræmic) the lower pole of the right kidney was located, and its depth was measured ultrasonically, before renal biopsy was performed. The actual depth of the kidney was measured at biopsy by means of a fine needle, the position of the lower pole of the right kidney being determined by inspection of an intravenous pyelogram in 14 patients; the remaining 6 were

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* Flaw-detector Model USM 1 available from Solus-Schall Ltd., Honeypot Lane, Stanmore, Middlesex.

uræmic and the lower pole of the kidney was visible on the plain X-ray in only 3 of these.

In 18 of the 20, kidney depth was determined to within 0·5 cm.; and in 17 the position of the lower pole was determined to within 1 cm. In 1 patient the position of the lower pole could not be determined on the plain X-ray but the probe needle inserted 2 cm. above the ultrasonically determined position of the lower pole entered kidney. In 1 patient the kidney was not identified because no deflection appearing on inspiration could be seen, owing to his rapid shallow respirations. Identification of the kidney at biopsy was very difficult because of the 5° maximal swing of the needle with respiration. The other patient in whom the position of the kidney was not found ultrasonically was 6 ft. $1^1/_2$ in. in height. The lower pole of his kidney was not found, because the probe was not displaced far enough caudad to lie over the lower pole, and so the kidney was not identified with certainty.

DISCUSSION

There are many interfaces which give ultrasonic reflections in the area of the renal angle—twelfth rib, transverse processes of lumbar vertebræ, lumbar fascia.[8] One can be sure that the kidney is the origin of a deflection only when the lower pole comes down on inspiration into the beam of sound waves emitted by the probe, and so gives a deflection on inspiration which is not seen on expiration, when the kidney moves out of the beam. Liver behaves similarly but is usually much further from the back. Kidney reflections are seen to pulsate synchronously with the radial artery if the patient stops breathing at the height of inspiration. In uræmic patients ultrasonic estimation of the kidney depth and position can reduce the amount of probing needed to find the kidney and so probably reduce both the discomfort and danger of renal biopsy in these patients. Some experience is needed to interpret the deflections caused by various interfaces, but this is rapidly acquired. The portable flaw-detector can be used unmodified and calibration is simple.

SUMMARY

The use of a simple ultrasonic flaw-detector is described to determine depth and position of kidney as an aid to renal biopsy. This method may make biopsy in uræmic patients more practicable.

Thanks are due to Dr. S. Baker for his help with the cadaver experiments; Mr. B. Bloom, B.SC., for discussion of the principles involved; Prof. D. A. K. Black for encouragement and reading the manuscript; and Solus-Schall Ltd. for lending the apparatus used.

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Reviews of Books

Darwin and the Naked Lady

Discursive Essays on Biology and Art. ALEX COMFORT. London: Routledge & Kegan Paul. 1961. Pp. 170. 18*s*.

READERS of *The Lancet* will not expect orthodoxy of Dr. Comfort. His unorthodoxy is, however, fairly orthodox for an intellectual radical of the day and more exciting than most. He is very intelligent: he has read almost everything which bears on his subject in at least five living and three dead languages: he has a lively wit: he is in favour of Matisse and the experimental method: he is against inhibitions, atomic weapons, and synthetic sherry. He begins by making a distinction between hard-centred and soft-centred writers. The first (Darwin, Freud, Shelley) assume that what we see is due to some intelligible process: the second (Bergson, Jung, Yeats) nourish the hope that the unknown is so far beyond our understanding that it is our part to relax in reverent awe. It is a talking point useful in argument and likely to make a polite parlour game. He examines Freud in terms of Darwin: the subconscious mind is as liable to natural selection as the femur. He is sympathetic and illuminating on the signs of the subconscious imagination in pictorial art long before the surrealists. He compares the romances of the Alexandrine Greeks with the sex-and-violence fiction of today and makes some horrid forecasts. He suggests that sexual gymnastics are likely to take their place among the western (with a small w) creative arts. After some directions for playing doyleys on the pianola he propounds an evolutionary theory of æsthetics and tells us that the New Guinea pidgin for destroy is *bagarimap*.

There is something here for everyone, but we should like to know who said that the best argument for Freud is that he makes intelligible sense of *Tristram Shandy*. And surely D'Annunzio was not dismayed but highly gratified by the effects of his pseudo-statements at Fiume? Dr. Comfort's style sometimes recalls the gypsy fiddler who rends our souls with an exciting air and some startling chords—and then ad-libs long enough for our attention to wander back to the goulash on our plate.

Neoplasms of Bone and Related Conditions

2nd ed. BRADLEY L. COLEY, M.D., attending surgeon (emeritus), bone tumour department, Memorial Hospital for Cancer and Allied Diseases, New York. New York: Paul B. Hoeber. 1960. Pp. 863. $30.

THE author of this book, internationally famous for his studies on bone tumours, may be said to have inherited his interest in the subject from his father. Certainly some of the most remarkable pages he has now written are those describing his father's researches with his "mixed toxins". In 1891 William B. Coley heard of a case of lymphosarcoma of the neck which recurred after three operations for its removal, and then permanently regressed after an accidental erysipelas infection. In an endeavour to reproduce this process, he treated a series of cancer patients with streptococcal cultures attenuated by heat, and later reinforced with a filtrate from growths of *Bacillus prodigiosus*.

Although results were sometimes very encouraging, mixed toxins are seldom used today. They still have a place though, Dr. Bradley Coley feels, in some cases of primary reticulum-cell sarcoma: and an investigation into the property, which many bacterial cultures possess, of causing hæmorrhage and necrosis in rapidly growing tumours, is still in progress.

Among the other points he makes are that Ewing's tumour is better treated by irradiation and chemotherapy than by amputation: and that though osteoclastomas respond well to irradiation (preceded by an aspiration, rather than an open, biopsy) and to curettage, no attempt to combine both procedures is permissible. It is depressing to learn that Dr. Coley, in all his long experience, has seen only one child under ten with an osteosarcoma saved by amputation. Now he seldom recommends such treatment, though he acknowledges that no other carries any prospect of cure.

This is a manual written by a clinician for clinicians. Used in conjunction with the pathological treatises of Ewing and Jaffe, it places at the surgeon's disposal the most authoritative possible advice on a subject where counsel is often divided and decision notoriously difficult.

Vertebrate Biochemistry in Preparation for Medicine

M. W. NEIL, PH.D., F.R.I.C., senior lecturer in biochemistry, London Hospital Medical College. London: Pitman Medical Publishing Co. 1961. Pp. 360. 40*s*.

THE shafts of wit which enliven this book almost disarm

criticism; yet there is much in it which calls for criticism or at least questioning. Addressing himself to the preclinical student, the author faced a choice familiar to many teachers of biochemistry. Should they continue to teach their subject as a branch (or twig) of physiology, restricting its scope to what seems strictly relevant to clinical medicine? Or should they break with tradition and try to instil at least an awareness of biochemistry as a wider, self-contained, and dynamic academic discipline? All biochemists—and most senior students whose scientific imagination has not been blunted by examinations—will incline towards the second course; and this is the alternative which the author has chosen. But at a price. Conscious of the overburdened preclinical curriculum, he has balanced the inclusion of a certain amount of advanced academic biochemistry against the omission of much orthodox material. It may be true that hormones, diet, and vitamins are better discussed in their proper context during the clinical years: but who is going to discuss them? That biochemistry should be taught as one of the basic sciences throughout hospital training is an admirable but still utopian suggestion: the further biochemistry advances the less equipped is the average clinician to provide students with even a rudimentary biochemical background. Moreover, is it not reasonable to stir the student's first interest in biochemistry by displaying its close links with clinical science? A halfway house surely exists between the ward sluiceroom and the research laboratory. At times Dr. Neil seems almost to go out of his way *not* to point a clinical moral.

Oddly, in view of his declared intention to teach biochemistry as a science in its own right, the best chapters are those in which he ranges widely (almost rhapsodically) over subjects of common interest to the pure biochemist and the clinical scientist. The very first chapter—a Biochemical Miscellany—arouses high hopes not only by the sweep of its contents but by its gay, almost racy style. Unfortunately the pace soon slackens and the style becomes plodding. A certain amount of dry, factual knowledge is, of course, essential for later flights of imagination; but one cannot help feeling that even this groundwork could have been made easier. As if the author himself had lost interest, at times his sentences become tortuous and jargon-ridden; and basic principles get submerged in secondary detail. But there is much on the credit side. Dr. Neil introduces his chapter on the Energy for Life with a bold and challenging statement; and, though he is there concerned with physical energy, he clearly believes that a capacity for sustained mental effort should be within the power of every university student. Many an undergraduate will be grateful for being treated as the owner of an alert, inquiring, and critical mind rather than as a primitive computor to be fed on predigested fragments of an examination syllabus.

Municipal Composting

A. G. DAVIES, F.A.P.H.I., M.INST.P.C. London: Faber & Faber. 1961. Pp. 193. 30*s*.

THIS is a book for the municipal engineer rather than for the medical officer of health or the treasurer. It makes a good case on the grounds of economy and convenience for the composting of the organic wastes in urban refuse as an alternative to tipping and other methods of disposal. It illustrates the advantages of the method from the experiences of communities at home and abroad. There is next to nothing about the dangers to health—if they exist. There is nothing about the economic return from the sale of organic fertiliser nor any quantitative argument which would persuade a farmer to make use of it. The pictures add a good deal to the price of this book without illuminating it.

Symptoms and Signs in Clinical Medicine (7th ed. Bristol: John Wright. 1961. Pp. 569. 45*s*.).—The sections on clinical pathology and radiology have been extensively revised, a new chapter on the history of medicine has been added, and there are many new illustrations. Most of these new pictures are an improvement on the old, but some of the colour photographs are disappointing. The size of the book has been increased by 60 pages, and it is now in danger of becoming a little overweight. It seems doubtful, for example, whether the very brief discussion on the diagnosis of neurosis serves any useful purpose, and the chapter on Fever could with advantage be considerably shortened. These are minor imperfections, and Dr. E. Noble Chamberlain's book continues to be a first-class primer for undergraduates. The price has gone up, but it is still very reasonable.

New Inventions

A SUCTION TUBE FOR AURAL AND DENTAL OPERATIONS

IN operations on the ears and teeth, when suction tubes are being used to clear the wound of blood, small fragments of bone find their way into the tube and often lodge in it. Blood clotting on these fragments soon makes the tube useless, and trying to clear the tube, or changing it, causes delay. To be sure that the bore of metal tubing is completely clean is impossible, especially if it is much bent. A dirty irregular lumen makes obstruction much more likely, as well as being undesirable for other reasons.

Rigid polyethylene ('Polythene') is a much more suitable material for suction tubes than metal or glass. Translucent, slightly flexible, boilable, and unaffected by any solution used for cold sterilisation of instruments, it is easily worked to any desired shape by simple methods. Thus a tube can be formed of convenient shape and visibly clean. An obstruction to the bore can be seen; this is likely to be at the tip of the tube, and can be wiped away or cut off.

The most satisfactory material for these tubes is rigid 'Portex' polyethylene tubing, 0·210 in. bore, and 0·365 in. outside diameter. Standard tubing, when drawn, tends to produce a very thin-walled tube which crumples easily if carelessly handled.

The tubing is worked by heating and drawing in the same way as glass, but at a much lower temperature. A 9-in. length is cut with scissors, and an inch at the centre of the tube is warmed by rotating it over a spirit-lamp flame until a transparent glassy-looking bubble is formed. The bubble is then drawn out into a tube of the desired length and diameter by steadily and gently pulling apart the unheated ends which are held at a suitable angle to the tube being drawn. The usual bubble will draw out to about a foot, but can be drawn further if required. It is wise to allow the tubing to shorten by about half an inch while still soft, thus releasing the elastic strain which would otherwise cause distortion when the tubes are first boiled. This tube will soon harden and can be divided to form two suction tubes whose narrow tips can be shortened as desired.

These narrow tips can then be still further drawn to produce tubes of any degree of fineness, though this is a little more difficult. A few minutes' work will produce a month's supply of tubes.

These tubes can be used many times, but tend to assume a brownish tinge after repeated boiling. Three points should be noted:

(1) The tubes should not be lifted out of boiling water with Cheatle's forceps since they are soft at this temperature and are pinched by the forceps.

(2) The tubes should not be autoclaved or they will melt.

(3) A boiler containing them should never be allowed to boil dry, since the detritus after this accident is almost irremovable.

This type of tube has been in use in several hospitals in this region for about four years and is undoubtedly an improvement on metal tubes.

'Portex' tubing is obtainable from Portland Plastics, Ltd., Bassett House, Hythe, Kent. It costs 1*s*. 6*d*. per foot.

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THE LANCET

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Iatrogenic Diseases of the Newborn

THAT one person's meat may be another's poison can be especially trying when the two individuals are connected by a placental circulation: thus the drugs taken by the pregnant woman may enter and upset her fœtus. Moreover, drugs prescribed in doses relatively safe for older children and adults may harm the newborn even when given in proportionate amounts. So many surprising examples of this danger, admirably reviewed by NYHAN [1] and LUCEY,[2] have been recorded in the past few years that it behoves all who care for the pregnant woman or the newborn infant to be on the alert for it.

Tolbutamide [3] has been blamed for the congenital malformations of infants of diabetic mothers. This has not yet been confirmed; but undoubtedly the androgens,[4] the androgenic progestogens,[5 6] and occasionally the synthetic œstrogens,[7] if given in early pregnancy, can masculinise the female fœtus. Malformation has followed attempted abortion with aminopterin,[8] and congenital goitre may result from treatment of the mother with anti-thyroid drugs [9] or with iodide-containing mixtures as recorded again, in our present issue, by Dr. ANDERSON and Dr. BIRD. The use of hexamethonium bromide for maternal hypertension has caused paralytic ileus in the fœtus [10]; while temporary nasal discharge, costal retraction, lethargy, and anorexia have been reported in newborn infants of mothers receiving reserpine during labour.[11] The thoughtless administration of large volumes of intravenous fluids to labouring women can certainly influence the plasma-sodium concentration and the tonicity of the fœtus, although there is still no direct evidence that this is harmful.[12]

The vitamin-K analogue, naphthaquinone, ' Synkavit ' (the diphosphoric acid ester of 2-methyl-1 : 4-naphthohydroquinone), is now known to cause hyperbilirubinæmia and even kernicterus in the newborn,[13 14] particularly in the premature,[15] when (on the false assumption that if a little of it does good then a lot must do much better) it is given in doses far exceeding the 1–2 mg. necessary for the correction of hypoprothrombinæmia, or when it leaks across the placenta after a really big dose has been given to the mother before delivery. It is directly harmful to red blood-cells even in vitro, and it may be more so in the presence of hypoglycæmia or when vitamin-E levels are as low as they are in prematures.[1] On the other hand it causes the abnormal breakdown of red blood-cells in which as a genetic defect the enzyme, glucose-6-phosphate dehydrogenase, is deficient and glutathione stability is altered. But in the low doses now recommended it should be harmless.

That redoubtable antimicrobial warrior, chloramphenicol, has habit of returning bloody but unbowed from the recurrent near-mortal wounds inflicted by his critics. At present this invaluable antibiotic is shunned by many because there is considerable evidence that it has caused the death of newborn infants.[16] Several observers, principally in the U.S.A., have described how babies, particularly prematures, have after a few days' treatment with chloramphenicol developed poor appetite, irregular shallow respiration, abdominal distension, hypothermia, flaccidity, ashen-grey cyanosis, and circulatory collapse, and have died. These signs can, of course, result from the infection for which chloramphenicol is given; and it is only fair to point out that the " grey syndrome " has usually appeared when this antibiotic has been prescribed for newborns in daily doses of 100 mg. or more per kg. body-weight, and that it has not been reported when the manufacturers' recommendation of 25 mg. per kg. daily for prematures and double this amount for full-term babies in the first week of life has been followed. The susceptibility of the newborn seems to lie in a failure of glucuronidation whereby relatively low doses produce effective or high plasma-levels of free chloramphenicol and excretion of the inactive glucuronide is reduced. This is a further example of enzyme immaturity; and here, as in the poor glucuronidation of bilirubin in neonatal hyperbilirubinæmia, a deficiency of glucuronyl transferase is important. A dose of 25 mg. per kg. daily is probably adequate not only for prematures but for all babies in the first week, and administration need only be twice daily. Thus although there has been a swing away from chloramphenicol, and even frank condemnation of it, its use continues in hospitals where it has been freely used for years in the newborn in low but effective doses without the " grey syndrome " having been observed. NYHAN [1] points out that similar problems of immaturity in relation to glucuronidation may affect the metabolism in the baby of thyroxine, hydrocortisone, and (more important) progesterone and morphine. The newborn is also deficient in the enzyme pseudocholinesterase [17]; and this may be of practical importance, since long-continued apnœa has been described where succinylcholine has been used in anæsthesia in the absence of normal enzyme activity.[18]

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High circulating levels of unconjugated bilirubin, due partly to glucuronyl-transferase deficiency, are associated with a risk of kernicterus which varies directly with the level and indirectly with maturity. An explanation of kernicterus at lower indirect-bilirubin levels after administration of the sulphonamide, sulphafurazole, has been offered by ODELL.[19] Unconjugated, toxic bilirubin is loosely bound with plasma-albumin and in this form may be less likely to cause damage. Sulphafurazole, however, as well as salicylate and caffeine sodium benzoate, competes favourably with bilirubin for the binding sites on the albumin molecule and can displace bilirubin from them. Thus the administration of sulphafurazole may, without altering the indirect-bilirubin level, cause a rise in free cerebrotoxic bilirubin. The possible danger of the long-acting sulphonamides in this connection is unknown, but their use has been discouraged.[2] Similarly a deficiency in the plasma-albumin level, as in prematurity, may so reduce the available binding sites for bilirubin that higher free levels develop. Certain neonatal tissues (again particularly in the premature) may be unusually susceptible to various substances. The classical example is the retina, which can be so disturbed by sustained high atmospheric concentrations of oxygen that retrolental fibroplasia results.[20] More simply, the newborn may be damaged because in a proprietary antibiotic mixture a high but harmless dose of one (for example, penicillin) selected by the physician is necessarily accompanied by a toxic dose of another (for example, streptomycin). Lastly skin contact with unlaundered marking-ink may produce severe methæmoglobinæmia.[21]

A pregnant diabetic woman on tolbutamide with or without insulin may receive sulphafurazole or chloramphenicol for a complicating pyelonephritis, cobalt and other hæmatinics for an anæmia, a salt-restricted diet and hydrochlorothiazide for toxæmia, copious intravenous fluids before delivery, and a large dose of synkavit to help reduce the risk of hæmorrhage in her premature baby. All the drugs prescribed by all concerned with each patient should be carefully recorded and their possible role in the ætiology of unexpected disorders in the infant should be carefully examined.

Hands and Faces

A SURGEON in his mask, gown, and gloves is, in popular imagination, the very embodiment of bacteriological cleanliness. The surgeon himself may wonder just how effective is his traditional uniform as a barrier between himself and the patient. All three items of the outfit have been studied in some detail, and two of them —gloves and masks—have lately been re-examined.

More than twenty years ago, DEVENISH and MILES[22] pointed out that, of the gloves used during an operation, about one in four was punctured without the surgeon's knowledge. Indeed, they attributed a serious outbreak of wound sepsis largely to infection through punctured gloves. This was not surprising in view of PRICE's[23] demonstration that the preoperative surgical scrub with soap and water reduced the number of bacteria on the skin by only about 50%. LOWBURY and LILLY[24] have studied the leakage of skin organisms through holes in rubber gloves. Members of their laboratory staff wore a punctured glove on one hand and, as a control, an intact glove on the other, for an hour after a routine surgical scrub with soap and water. By an ingenious method, they then counted the number of bacteria coming through the holes during simulated surgical manipulations. From their results it can be calculated that perhaps 20–30 bacteria per minute are squeezed out of each hole while a punctured glove is being used. What this means in terms of risk to the patient can only be conjectured; but, since *Staphylococcus aureus* and other pathogenic species will often be among the emerging organisms, any practicable measure to reduce the leakage seems worth taking. One way is to reduce the frequency of punctures by wearing the stronger latex glove instead of the more popular solution-dipped glove; another, which deserves to be more widely known, is the use of an electrical device that reveals punctures that have occurred during an operation.[25] But, with or without these precautions, the surgeon can reduce the number of organisms escaping through punctures by supplementing his preoperative scrub with an effective skin disinfectant. LOWBURY and LILLY investigated several of these and found that the bacterial leak was reduced to about a tenth by using 2% hexachlorophane soap for the scrub itself, or by a three-minute rinse in 70% alcohol after the scrub. The results were still better when ' pHisohex ' (which contains 3% hexachlorophane) was used for the scrub, or when 0·5% chlorhexidine (' Hibitane ') was added to the alcohol rinse. A glove-powder containing neomycin and bacitracin was also very effective, but the wisdom of using antibiotics in this way may be doubted. Those who choose to use hexachlorophane should remember that it is a slow-acting but cumulative disinfectant, and is most effective used not only for the surgical scrub but also, in toilet soap, for all personal ablutions. The efficacy of hexachlorophane has been confirmed by BEILBY and THOMPSON[26] in a practical trial in a busy theatre, where pHisohex reduced the bacterial population on the fingers of six surgeons more than did several other popular skin disinfectants. Unfortunately, this otherwise valuable trial was marred by a fault that has invalidated so much work on disinfectants—namely, failure to incorporate in the culture-media a neutralising substance for each disinfectant used.

For an investigation of masks, SHOOTER et al.[27] persuaded 129 volunteers to put their heads into a special chamber, with culture-plates arranged round them to catch the larger contaminated particles, and a slit-sampler for counting the smaller ones. Their results confirmed the finding of DUGUID and WALLACE,[28] and of HARE and THOMAS,[29] that the expulsion-rate for

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29. Hare, R., Thomas, C. G. A. *Brit. med. J.* 1956, ii, 840.

Staph. aureus, even without a mask, was very low during silence or quiet speech. When a mask was worn, quiet speech, compared with silence, caused no detectable increase in the expulsion of staphylococci. Several types of mask were studied, and, because of the low expulsion-rate for staphylococci, comparison of the masks was based on counts of general respiratory-tract organisms, whether pathogenic or not. For protection of the area in front of the face, there was no significant difference between the performances of fabric " filter masks " and paper or paper-insert " deflector masks ". Both types were apparently less effective for the smaller particles that tend to escape backwards, particularly from deflector masks; but the number of particles that escaped even in this way was very small, and in a properly ventilated theatre they would be carried away without drifting into the central area. THOMAS,[30] in experiments during normal speech with and without masks, found that filter masks reduced contamination of exposed plates by 95·8% and that deflector masks did so by 96·4%. Slit-sampler counts for smaller particles gave efficiencies of 97·8% for the filter and 82·2% for the deflector masks. There was no deterioration of efficiency in either type of mask during three hours' continuous use nor, in the non-disposable cotton masks, after repeated laundering. It is occasionally suggested that " absolute filters ", of similar design to a war-time gas mask, should be worn during operations. Surgeons will be relieved to know that this seems unnecessary. It also seems that the choice between filter and fabric masks can depend on personal preference.

For his experiments with speaking subjects, THOMAS asked his volunteers to read HILAIRE BELLOC's *Cautionary Verses*. This is significant because a few words of caution are needed. These studies with masks showed that quiet speech involves no great increase in the risk of infection. But, as Sir REGINALD WATSON-JONES [31] has said, even a small increase is unacceptable, and during an operation even quiet conversation should be restricted to essentials. And THOMAS found that both filter and deflector masks were notably ineffective when tested by an explosive utterance of a type not unknown in operating-theatres.

British Medical Dictionary

THE French Academy took forty years to complete their Dictionary, and Dr. JOHNSON laboured over his one-man masterpiece for nearly eight. In a preface to the *British Medical Dictionary*, published this week,[32] Sir ARTHUR MACNALTY, the editor in chief, looks back on the work of fourteen years and acknowledges the collaboration of more than a hundred specialists and the help of an expert administrative staff. Their joint achievement is a volume of 1680 pages, produced with the dignity appropriate to a major work of reference but also so skilfully arranged and printed that it is a pleasure to consult. To get the full measure of such a book will need many years of continuous use; but clearly it is going to be a great help to all of us who are less than omniscient in the use of medical words.

To publish a book of this kind requires special courage, because many readers expect it to be literally perfect from the beginning and they are disproportionately disappointed if they find it anything less. But in point of fact imperfections are probable in the earlier editions of any standard work, and they are inevitable in a medical dictionary produced at a time like this, when every kind of specialist uses fresh knowledge and fresh words almost every day. Dr. JOHNSON happened to have a genius for it; but how many of the rest of us would confidently define 6 words, let alone 6000? And this is only a beginning. For whereas JOHNSON could print his own definitions, the organisers of a new dictionary have to depend on those supplied by a very large number of people doing many different kinds of work, whose individual opinions have to be made to sound like the consistent voice of Authority. Moreover the reader, demanding that the dictionary should be comprehensible, will be surprised if it is not also comprehensive, as judged by inclusion of everything in medicine that he himself happens to know. Frankly, this is impossible. And if (in the manner of reviewers) we now remark on some things the dictionary has not done, this does not mean that we are any the less grateful for what it has done so well.

In its first edition the chief function of such a work is to clarify orthodox medical terminology: along the new frontiers, where aggressive little specialties proliferate and neighbouring sciences pour in their nascent jargon, it is a less informative guide.

Perplexed registrars will still have to rack their brains for the meaning of penetrance, non-disjunction, trisomy, and hypoploidy, and sorely tried medical secretaries will continue to be unorthodox over Papanicolaou, Duffy, Kell, mann, Szent-Györgyi, Hank's solution, and HeLa cells. Hæmatologists—inveterate word-coiners—are granted their Christmas disease, but not their Stuart-Prower or Hageman factor or even haptoglobin. Biochemists may be saddened by finding no reference to thymol flocculation, transferrin, cæruloplasmin, and cephalin cholesterol. To expect a codification of modern statistical jargon might be to ask too much, but many would have welcomed entries on χ^2, double-blind trial, and t test. Virologists, representing one of the youngest and most vigorous of backroom sciences, might justly argue that many obsolete bacteriological terms could have been replaced by those now widely used in tissue culture. Even in clinical medicine time has clearly been the enemy. Comparatively few syndromes of less than six years' standing (e.g., Hartnup, maple-syrup, Zollinger-Ellison) have been included; and even some much older (e.g., Sheehan and Peutz-Jeghers) have yet to be admitted. The entries for many others (e.g., Turner, Klinefelter, mongolism) will have to be revised in the light of recent or not-so-recent discoveries. And " autoimmunity " and " clones " will have to cast off their bacteriological shackles.

We mention such deficiencies as an indication of the almost unlimited range of subjects on which a dictionary may be asked—reasonably or unreasonably—

30. Thomas, C. G. A. *Guy's Hosp. Rep.* 1961, **110**, 157.
31. Watson-Jones, R. *Brit. med. J.* 1960, i, 1501.
32. British Medical Dictionary. Edited by Sir ARTHUR MACNALTY. London: Caxton Publishing Co. 1961. Pp. 1680. £10 10*s*. The first supplement will be supplied gratis to each purchaser of the Dictionary, but thereafter a small charge will be made.

to give the latest information. What is difficult, we have been told, can be done at once; and, broadly speaking, the *B.M.D.* has done it. For the impossible (which takes a little longer) we may look to the annual cumulative supplements which are promised.

In its general construction the new dictionary raises an interesting and quite important question to which there seems to be no convenient answer. Edited by a historian, it gives the names of a great many people, past and present. But, being a dictionary and not an encyclopædia, it is concerned primarily with the things that people have invented or discovered; and even the most eminent are included only if they happen to have earned eponymous fame. Maybe this was right; but a futile search for such hallowed names as Paré, Semmelweis, O. W. Holmes, and Banting leaves one sighing for a little more cult of the personality. Fortunately many of the really great get a place because they have managed to attach their names to something; but Pasteur's claim rests on six rather oddly assorted items, and Lister (though he gets justice under Listerism) has nothing under his own name except his radial tubercle and a ferocious-sounding antiseptic mixture. Similarly, an Australian parasite notorious for causing an itchy dermatitis earns Leeuwenhoek an entry in parenthesis; but Linacre, Goulston, Lumley, and Morton the anæsthetist, having no such fortuitous legacies, lose the places one would like them to have in this Valhalla.

Another problem of lexicography which this dictionary does not quite solve is that of derivations. How far should they be taken? To the ordinary reader—now so seldom a classicist—it may seem that the *B.M.D* takes them far enough; but even he might often learn something from the change of use that etymology may reveal. To be told that "icterus" comes from the Greek "ikteros", and "cretin" from the French "crétin", is of little assistance unless one is given a hint of the original meanings. Admittedly, to compress a long story accurately into a single entry may be far from easy; and some of the derivations which have been included could in fact be challenged—e.g., that "obstetrics" comes from "obstetricare", that "antimony" originates in Latin, or that "chancre" in French is "canker".

But all these remarks really do no more than illustrate again that the care and scholarship that have gone into this work make the reader demand at every point the highest standards and cause him to complain whenever complaint seems possible. Our own criticisms, indeed, seem rather of the kind a tourist is apt to make after doing half the Continent in a fortnight. The roads in Spain were calculated to break his motor-car; the baby food in Italy was anything but wholesome; and the beds in Bosnia were not what he was accustomed to. Yet he will probably be observed returning to the scenes of all these murmurs; and so shall we. Despite its appearance of finality, the *British Medical Dictionary* has a little of the fallibility of its youth and its merely human origin; but this should make it the easier to live and work with. Its 1680 pages are packed with useful and fascinating information.

Annotations

POLIOMYELITIS

AT the seventh symposium of the European Association against Poliomyelitis, held in Oxford on Sept. 17–20, Prof. M. Chumakov (U.S.S.R.) and his colleagues made a notable contribution. In summary their findings are as follows:

In 1959–60 in the Soviet Union and several other countries mass oral immunisation was carried out with live vaccine prepared from Sabin attenuated strains. In the U.S.S.R. the vaccine was given in 1959 to about 13,500,000 persons and in 1960 to about 77,479,000, mostly aged 2 months to 20 years (in some republics and regions up to 45–55 years). In addition, live vaccine from Sabin strains was given in 1959–60 to about 13,150,000 children under 15 years of age in Albania, Bulgaria, Hungary, the Democratic Republic of Viet-Nam, the German Democratic Republic, the Korean People's Democratic Republic, Czechoslovakia, and China. In 1960 the majority of vaccinations (over 95%) in the U.S.S.R. were performed with live vaccines incorporated into dragee-candy (vaccines of a single virus type of types I+III, and of types I+II+III). Each piece of dragee-candy contained one inoculation dose.

Large-scale use of oral live vaccine from Sabin strains in the U.S.S.R. and some other countries has confirmed the complete safety of this preparation for man, the absence of any untoward reactions in the vaccinated, and the absence of epidemiological or clinical evidence of reversion to pathogenic properties in vaccine poliovirus strains circulating among the population in areas of mass vaccination.

As a result of two years' observations in the U.S.S.R. it has been proved that large-scale oral administration of live poliovirus vaccine from Sabin strains represents a most effective method of specific poliomyelitis prophylaxis, with a regular, rapid, and pronounced effect in terms of prevention of poliomyelitis epidemics. This was confirmed in 1960 by comparison of monthly poliomyelitis incidence-rates in areas of the U.S.S.R. where candied live vaccine had been used on a large scale and in areas where only inactivated Salk vaccine had been widely used. Administration of candied live Sabin vaccine led to a sharp reduction in poliomyelitis incidence and complete prevention of a seasonal rise in incidence during summer and autumn months. Inactivated Salk vaccine also reduced considerably the number of paralytic cases in the vaccinated compared with that in the unvaccinated, but on the whole it did not affect the epidemic process and did not prevent the usual seasonal rise in incidence in areas where it was given.

These observations confirm that it may be possible by means of oral live vaccine to eradicate poliomyelitis epidemics in a large country. The time is not far distant when poliomyelitis epidemics will have been done with in the U.S.S.R. Complete eradication of sporadic poliomyelitis cases based on elimination of circulation of the causal agent appears to demand tenacious efforts for a number of years.

This contribution set the stage for a vigorous and informative debate between the proponents of the Salk-type killed vaccine given by injection and of the living attenuated vaccine given by mouth. There are three main questions to be considered about these vaccines. Are they safe? Are they effective? Are they easy to administer? As regards safety, on one side it was argued that it was never safe to give a live virus; for it was impossible to tell what harm might come of it, either by return of virulence or by the accidental inclusion in the vaccine of other viruses. In reply it was said that theoretical arguments were of no importance when practical experience had shown that harm did not result, and that experience with well over 100 million vaccinations constituted as large

a field trial as could possibly be required. The efficacy of both types of vaccine was demonstrated by the almost universal experience that when a large proportion of the susceptible population was vaccinated the incidence of poliomyelitis fell precipitously. Nevertheless, serious epidemics of poliomyelitis continued to arise in communities where vaccination with killed vaccine had been widespread. This had happened in Europe, in North America, and in certain parts of the U.S.S.R. where killed vaccine was used. In contrast, in those areas of the U.S.S.R. and elsewhere where live vaccine had been used the seasonal epidemics had disappeared, leaving only the sporadic cases occurring at any time of year. To the proponents of the live vaccine it seems right to run a risk of an undefined misfortune which has not been detected in practice, in order to guard against the known risk of epidemics of poliomyelitis. Compared with safety and efficacy, ease of administration may seem a minor matter. With killed vaccine, however, two injections are required at first, followed by a booster injection every one or two years; and it is doubtful whether parents will submit their children to this, especially when poliomyelitis ceases to be "news". Live vaccine, on the other hand, is neither unpleasant to take nor difficult to administer. Such were the arguments. The advocates of each vaccine were unable to convert one another, and countries already launched on a vaccination programme with one type will probably be slow to change to the other. In Japan, where poliomyelitis has recently become a serious problem, the present campaign is with live vaccine.

Other subjects discussed at this symposium included the diseases due to enteroviruses other than those of poliomyelitis—notably the ECHO and Coxsackie groups of viruses. It is now plain that both these groups can cause lymphocytic meningitis with or without paralysis, and that the disease may be indistinguishable from non-paralytic and paralytic poliomyelitis. The diagnosis of poliomyelitis can therefore no longer be accepted without virological confirmation. The ECHO and Coxsackie viruses can also cause neurological disorders, including acute ataxia and encephalitis; and in such cases both fæces and cerebrospinal fluid should be examined virologically. Orthopædic problems and the treatment of respiratory paralysis were also discussed, but their importance in poliomyelitis is rapidly dwindling with the success of vaccination. The experience reported from the respiration unit in Oxford is probably typical—namely, that poliomyelitis is now rarely an indication for artificial respiration but that the techniques learnt in treating poliomyelitis are proving life-saving in other conditions with a better ultimate prognosis.

At the conclusion of the symposium the national delegates elected Dr. W. Ritchie Russell, director of the department of neurology, United Oxford Hospitals, as president in succession to Prof. H. C. A. Lassen of Denmark.

PORTACAVAL ANASTOMOSIS

THOUGH an Eck's fistula was first undertaken more than half a century ago, the making of venous shunts for portal hypertension really dates from a report in 1945 by Blakemore and Lord.[1] At first a vitallium tube was used for the anastomosis, but within a few years a suture technique became standard practice. For cases of intrahepatic obstruction with a patent portal vein many surgeons have favoured an end-to-side anastomosis between the portal vein and the inferior vena cava, thus diverting all the portal blood from the liver but closing the portal vein as a possible outlet of blood from the liver. Early results suggested that this operation gave better results than a splenic-vein/renal-vein anastomosis as regards prevention of gastrointestinal hæmorrhage, but that it was more likely to be followed by cerebral symptoms. The immediate mortality depends as much on the selection of cases as on the operative technique and postoperative management. Thus Riddell and Jones[2] have reported from Manchester a consecutive series of 33 shunts without hospital mortality, and in our present issue Prof. Milnes Walker and his colleagues in Bristol report a hospital mortality of 5% in a series of 150 end-to-side portacaval anastomoses.

In Boston McDermott et al.[3] analysed 237 cases in which either splenorenal or portacaval shunts had been established, excluding those in which the operation was done as an emergency and a few in which other types of anastomosis were made. Rather more than two-thirds of the patients had splenorenal shunts, and in the years 1955–58, by which time considerable experience of both operations had been gained, this operation carried a considerably higher operative mortality than the portacaval shunts. After splenorenal shunts the fall in portal pressure was not nearly so satisfactory as after portacaval anastomoses. Recurrent bleeding was commoner in those with splenorenal shunts (26%) than in those with portacaval shunts (15%); but there was practically no difference between the two groups in the incidence of encephalopathy. Patients with splenorenal shunts, including 18 with extrahepatic block, had a slightly better five-year survival-rate—namely, 73% of those who survived the operation and left hospital, compared with 65% for the portacaval group—but the ten-year survival-rate was 43% for both groups.

In their article this week Milnes Walker and his colleagues review the results of 50 operations of end-to-side portacaval anastomosis performed at Bristol between five and eleven years ago, and they find that there was a 6% hospital mortality and that 70% of the whole group are still alive. Of the 35 survivors 29 lead normal lives; but 5 of the other 6 are severely incapacitated by encephalopathy.[4] Severe recurrent hæmorrhage has taken place in only 4—which contrasts strongly with the preoperative course of the group, of whom all but 1 had had massive hæmatemesis.

In portal hypertension leucopenia and thrombocytopenia are common. Removal of the spleen as part of a splenorenal anastomosis seems to be beneficial, for in 36 out of 42 cases in the Boston series the blood-picture reverted to normal after splenorenal anastomosis, whereas in the Bristol series the low blood figures persisted after portacaval anastomosis despite reduction in the size of the spleen, which became impalpable in 70% of the patients.

Both these series are selected groups, and hence it is impossible to compare them with others treated without operation; but from the long-term results it is clear that the diversion of some or all of the portal blood from the liver does not cause any serious deterioration in liver function despite the reduced total liver blood-flow. The most serious consequence is the increased risk of portal systemic encephalopathy; but when this is severely

1. Blakemore, A. H., Lord, J. W. *Ann. Surg.* 1945, **122**, 476.
2. Riddell, A. G., Jones, W. K. *Brit. med. J.* 1961, i, 928.
3. McDermott, W. V., Palazzi, H., Nardi, G. L., Mondet, A. *New Engl. J. Med.* 1961, **264**, 419.
4. Read, A. E., Laidlaw, J., Sherlock, S. *Lancet*, 1961, i, 961.

incapacitating, and the patient is otherwise in reasonably good health, it is justifiable to consider colectomy, for the colon is the source of the protein-breakdown products which lead to this syndrome. (A dramatic success has been reported by Atkinson and Goligher.[5]) In the Boston series 15% of the patients followed had peptic ulceration, and in 6 this led to fatal hæmorrhage. Despite these complications, portal systemic shunt operations are at present the most effective means of preventing death from hæmorrhage in patients with portal hypertension.

PERIPHERAL VASCULAR RESISTANCE

ARTERIAL blood-pressure depends not only on cardiac output but also on peripheral vascular resistance, and increasing attention is being paid to the nervous and humoral factors that influence this resistance. The nervous factors act through a reflex arc [6] of which the motor side consists of the autonomic vasomotor nerves. The afferent side comprises two functional groups. There are nerves whose stimulation tends to reduce blood-pressure, of which the principal examples are the nerves supplying the baroreceptors in the carotid sinus and elsewhere in the great vessels. The other and larger group comprises those nerves whose stimulation tends to raise blood-pressure. A convenient experimental test involving this group of nerves is the " cold pressor test " in which one hand is immersed in ice-cold water.

Guttman and Whitteridge [7] investigated the increase in blood-pressure which may result when the bladder is distended. Koster and Bethlem [8] have studied patients with spinal-cord lesions in order to determine the central pathways concerned in vascular reflexes. They find that in the resting subject peripheral vascular resistance in the splanchnic area is particularly important. In patients with cord lesions at T11 vascular reflexes are normal; but when the cord lesion is above the origin of the splanchnic nerves (T6–7) blood-pressure changes little in response either to the cold pressor test of the hand or to emotion. Similarly orthostatic hypotension is never observed with lesions below T11 but is prominent with lesions above T6, because the descending pathway in the cord which normally stimulates the splanchnic nerves is interrupted. Distension of the bladder will, however, produce a rise in blood-pressure in patients with a lesion above T6, indicating that this is a spinal reflex one of whose major efferent pathways is the splanchnic nerves. In health the increase in blood-pressure is largely inhibited by baroreceptors acting through the brainstem and descending pathways in the spinal cord.

From lesions of the cervical cord we can learn about the central course of the baroreceptor reflexes. The afferent pathway from the carotid sinus is mainly the glossopharyngeal nerve, but from baroreceptors in the aorta and other great vessels some afferent connections enter the spinal cord. Koster and Bethlem describe evidence suggesting that some of these afferent fibres pass up the spinal cord close to the midline, whereas the efferent tracts from the brainstem pass down the cord more laterally.

Several workers [9–11] have observed sustained hypertension in patients who have had poliomyelitis. Hypertension is correlated with degree of muscle wasting, and the loss of muscle may make it impossible for the vasomotor reflexes to keep the peripheral resistance as low as normal. Ostfeld [11] measured the peripheral resistance in three cases and found it to be high. In acute polyneuritis, however, the opposite situation may occur; for in severe cases the vasomotor nerves are paralysed, and therefore reflex control of peripheral vascular resistance ceases. The blood-pressure can be maintained only by an increase in cardiac output or by humoral mechanisms, and the patient's condition may be critical. This is a genuine example of peripheral vascular failure—a phrase which is commonly misused. In contrast to the peripheral vascular paralysis of polyneuritis, there are many conditions, such as acute blood-loss, in which the peripheral vessels contract vigorously and the limbs become cold and the skin mottled. This peripheral vascular contraction is an important compensatory mechanism, and it is incorrect to describe it as peripheral vascular failure.

5. Atkinson, M., Goligher, J. C. *ibid.* 1960, i, 461.
6. See *ibid* Aug. 19, 1961, p. 474.
7. Guttman, L., Whitteridge, D. *Brain*, 1947, **70**, 361.
8. Koster, M., Bethlem, J. *Acta. psychiat. neurol. scand.* 1961, **36**, 347.
9. Vickers, H. D. *N.Y. St. J. Med.* 1940, **40**, 55.
10. Zimanyi, I., Prolaszka, M., Szondy, M., Ormai, S. *Acta. med. scand.* 1959, **164**, 497. See *Lancet*, 1959, ii, 120.
11. Ostfeld, A. M. *Arch. intern. Med.* 1961, **107**, 551.

TREATMENT OF PARKINSONIAN CRISES

THE postencephalitic type of parkinsonism is often characterised by sudden episodes of motor and behavioural disorder as well as by the better-recognised persistent tremor, rigidity, and slowing of movement. The best known of such crises—oculogyric crises—consist in sudden forced deviation of the eyes, usually upwards, often with an accompanying emotional storm, and sometimes with evidence of visual hallucination. Other episodic features include autonomic changes such as sweating, tachycardia, or (less often) bradycardia or upsets of respiratory rhythm. More often than not these are accompanied by acute anxiety; sometimes this occurs on its own as a sudden panic state. Such attacks are presumed to represent sudden excessive abnormal discharge of autonomic centres—" epilepsy " in Jackson's sense. There may also be episodic motor disturbances such as the akinetic attack for arrest phenomenon.

These symptoms are often very distressing to the patient, but their treatment has not received much attention. They do not respond much to the usual remedies for parkinsonism; and, when they develop, phenobarbitone is customarily added to the drug regimen. Onuaguluchi [12] has explored the use of intravenous sodium phenobarbitone in doses of 2–3 mg. per kg. body-weight as immediate treatment for a crisis. This apparently terminates both oculogyric and some autonomic attacks. Since these may last for hours and can cause acute distress, this remedy is well worth trying. Unfortunately prophylaxis, whether by barbiturates, phenytoin, amphetamine, or other drugs, seems relatively ineffective. Possibly some of the newer thymoleptic drugs may prove more helpful.

12. Onuaguluchi, G. *Scot. med. J.* 1961, **6**, 368.

INDEX TO THE LANCET

FORMERLY the index was sent only to those who asked for it, but now it goes to all subscribers. The index and title-page to vol. I, 1961, which was completed with the issue of June 24, is enclosed with each copy of our present issue.

As we may not be able to supply indexes to binders, orders for binding the collected issues are best deferred until the index can be sent with them.

Special Articles

"OUTPATIENTS EXTRAORDINARY"

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THE structure of the National Health Service separates the general practitioner from the hospital medical staff, and the gap between them grows wider and wider. The remedies usually suggested are (1) that all intending consultants should have first-hand experience of general practice, or (2) that some sort of part-time hospital appointments should be offered to practitioners. The disadvantages of both ideas are obvious.

Before the days of the N.H.S., when a second opinion was requested it was normally given after one consultation. A series of investigations or a course of treatment was recommended, but the specialist did not expect to see the patient again unless unforeseen circumstances arose. Nowadays, however, with the growth of the provincial hospital services and the increased complexity of the specialties, the situation has changed, and it is accepted practice for the patient to be followed up. For this there are three main reasons. Firstly, the consultant wants to follow the course of a condition under treatment, now that he can do so without expense to the patient. This may lead to the diabetic or hypertensive being seen at intervals throughout his life. Secondly, patients may have to be seen again so that the results of treatment can be evaluated statistically. Finally, in certain cases, the risk of litigation may lead the consultant to make assurance doubly sure by seeing the patient once again before discharging him.

PRACTITIONER AND HOSPITAL

Round the small country town of Petworth some 6000 patients are served by a partnership of four doctors working from a central surgery. The area covered is a rough circle centred on the town and with a radius of about six miles. The nearest general hospitals—at Chichester, fifteen miles away—are extremely difficult to reach by public transport from the periphery of the practice. A small cottage hospital is staffed by the partnership, and consequently we deal with many problems that elsewhere might be referred directly to a general hospital.

The part of West Sussex served by the Chichester hospitals has a population of about 120,000. It has a varied character and is composed of seaside resorts, market towns, and many farming communities. There is some light industry.

Table I, prepared from the report of the Chichester Group Hospital Management Committee for the year ended March 31, 1960, and from our practice records for the same period, shows that the Petworth practice is more self-sufficient than most. Nevertheless the Chichester hospitals performed nearly as many items of service per head of population, as this particular practice. The conclusion drawn must surely be that, when a patient registers with a general practitioner, he also in a sense registers with the local hospital.

TABLE I—PRACTICES OF CHICHESTER HOSPITALS AND PETWORTH PRACTICE

—	Chichester hospitals	Petworth practice	Referred by Petworth practice
Population of area served	120,000	6000	6000
New cases seen in 1960	54,000	4380	870
Items of service performed	286,000	25,000	2500
Approximate number of items per head of population	2·4	4·2	0·4

TABLE II—ANALYSIS OF CASES SEEN IN PETWORTH CLINIC FEBRUARY, 1960–FEBRUARY, 1961

Provisional diagnosis	New cases	Follow-up attendances				
		One	Two	Three	Four	Five
Cardiac disease	17	..	1	1	..	..
Thyrotoxicosis	7	3	..	1	..	..
Hypertension	3	..	1	..	..	..
Epilepsy	4	..	..	..	..	..
Hypocalcæmia	1	..	..	..	..	..
Hypoglycæmia	1	..	..	..	..	..
Sarcoidosis	1	..	..	..	..	..
Peptic ulcer	3	..	..	..	..	..
Subarachnoid hæmorrhage	1	..	..	..	..	..
Cushing's disease	1	..	..	..	..	..
Parkinson's disease	1	1	..	..	..	..
Polyarthritis	1	..	..	..	..	..
Diabetes	..	4	1	1	..	1
Bronchiectasis	..	1	..	..	..	..
Giant-cell arteritis	..	1	..	..	..	..
Rheumatic fever	..	1	..	..	..	..

TABLE III—PATIENTS SENT FROM THE CONSULTATION CLINIC TO HOSPITAL FOR FURTHER INVESTIGATION

Admissions for investigation	1
Electroencephalograms	3
Radioiodine treatments	2
Referred to hospital outpatient department	1

It might be thought from this that the general practitioner will eventually be relegated to the status of a glorified first-aid worker, whose main function in life will be to detect the patients who are probably ill and refer them to hospital for further investigation and care. In this article I describe another solution, which leaves the practitioner as the arbiter of the overall care of his patient, while benefiting patient, consultant, and the State.

THE PETWORTH SCHEME

Last year, when the practice moved its surgery premises to a more commodious building, one of the Chichester consultant physicians suggested that monthly clinics should be held in the new surgery for the patients of the practice. This offer was accepted enthusiastically and the sessions have now been held for more than a year. Since the only diagnostic equipment available was that normally found in any surgery, together with a portable electrocardiograph, some care was taken at first to select what were thought to be suitable cases. But now virtually all patients needing a general medical opinion are seen in the clinic. Table II shows the range, while table III suggests that most patients who were later seen elsewhere would have fared no better if they had gone straight to a general hospital.

The sessions are organised much like outpatient sessions at hospital. Beforehand, a list of the names and addresses of the patients, old and new, is sent to the outpatients secretary at Chichester. She makes up a standard hospital record folder and gives it to the consultant to bring with him. In the case of a new patient, instead of the usual letter of application, the history and findings are typed on an outpatient record sheet and inserted in the notes. The consultant has only to add his own comments and any new findings to these notes.

The consultations are held in a room large enough to accommodate the consultants and as many of the partners as are able to attend. The practitioner presents his own case and brings up any special difficulty he may have had. Next, the patient is invited in and interviewed by the consultant. He then goes to another room for the examination. After discussion between consultant and

practitioners he is seen again and the opinion is given. Afterwards the practitioner gets the usual formal letter embodying the consultant's findings and opinions.

A special feature of the session is the tea-break. This is set aside for discussion of patients not actually asked to attend for formal opinion. Off-the-record advice and encouragement is sought in much the same manner as it is sought by the junior staff in hospital on cases they feel otherwise able to manage by themselves. A rather flamboyant example might be cited. A diagnosis of toxoplasmosis was suggested by the consultant after hearing details of the case. Tests were performed and this diagnosis was proved. The patient was treated and recovered, having seen no one but his own practitioner.

ADVANTAGES

As yet we have encountered no disadvantages to the scheme while the advantages are many.

The *patient* is saved a tedious and time-consuming journey. The discussions of the tea-break may dispose of his problem without his even attending, and they will certainly lessen his liability to recall for follow-up. He sees the consultant in familiar surroundings and has the moral support of the presence of his own doctor, who, he feels, is taking a personal interest in his case. He is less likely to think there is any great difference in kind between "hospital doctors" and ordinary doctors, and so is much more likely to have respect for, and benefit from, advice given by either of them. He will not be the unfortunate recipient of conflicting opinion.

The *practitioner* benefits enormously, acting as he does as a sort of outpatient registrar. The discipline of preparing his cases for presentation prevents his clinical approach from becoming too sloppy. The teaching and demonstration help to keep him up to date with advances in medicine, and they are all the more forceful because the subjects are his own patients. The direct contact he has with the consultant enables him to pose his problems with a great deal more force and clarity than is ever achieved by a formal letter. With his special knowledge of the patients' temperament and domestic circumstances, he is in a position to advise the consultant on the adverse affect these might have on any line of treatment. The opinion that the patient receives will have already had the practitioner's approval. Most important of all, he no longer loses sight of a patient, perhaps for months at a time, who is attending hospital follow-up clinics.

The *consultant* receives the mental stimulus always given to the teacher by the taught. He learns at first hand the problems that are peculiar to general practice and is given a deeper insight into the patients' background than is normally obtained from purely hospital practice.

The *hospital* gains in three ways. The congestion of the outpatient department is to some extent reduced. There is less demand on the services of the already overtaxed junior medical staff who are normally responsible for follow-up clinics. Thirty minutes' consultation, followed by some investigations, are the necessary and inevitable result of a formal request for advice; but all this can sometimes be avoided by an informal chat during the tea-break.

Apart from any saving already implied, there is a large reduction in the cost of transport. Many patients who are able to make the short journey to the surgery unaided could reasonably ask for a car if they had to go to the hospital. Those who do need a car in any case have of course much shorter and therefore cheaper journeys.

OTHER SPECIALISTS

The practice has also benefited for more than five years from the advice and services of two other consultants:

An ophthalmologist holds refraction clinics weekly in the surgery, but he is always willing to see patients elsewhere or give advice on any problems in his particular field.

Once a fortnight a pathologist comes to the surgery to collect specimens, usually blood samples. The practitioners run through the request forms with him, explaining the reason for the request or seeking his opinion on the most illuminating tests and the significance of the results in the more obscure cases.

So successful have the arrangements been that they have attracted the interest of other consultants in the group, and it is hoped that they too will see their way to holding sessions in the surgery or the cottage hospital.

CONCLUSIONS

The general public nowadays have almost as much attention from the hospital services as they do from the family doctor. If he is to maintain his vital position in the structure of the health service, the general practitioner must keep closer contacts with the hospitals and the services they provide.

During the past year an outpatient session held in a country surgery has proved beneficial to all concerned. The scheme is one that could be much more widely applied, making a useful contribution to medical practice in this country.

Conferences

GYNÆCOLOGY AND OBSTETRICS

FROM A CORRESPONDENT

IN the impressive setting of the Wiener Stadthalle the inaugural session of the 3rd World Congress of the International Federation of Gynæcology and Obstetrics took place on the morning of Sept. 4. The president of the Congress was Prof. T. ANTOINE (Vienna).

The opening oration on the Viennese School of Obstetrics and Gynæcology: Its Spirit and Achievement was given by Miss ERNA LESKY. She traced the historical connections linking the Vienna school with gynæcological and obstetric progress; from the story of the first gynæcological laparotomy in 1549 (which Paul Dirlewang performed for a ruptured extrauterine pregnancy); the achievements of Semmelweis (1818–65) in combating puerperal pyrexia; the surgical contributions of Billroth (1829–94) and the pioneer work of Schauta (1849–1919) and Wertheim (1864–1920), the originators of modern operative methods for uterine carcinoma.

About 2500 delegates from 53 countries attended the congress. Representatives from eastern Europe were present (though fewer than originally planned). The main subjects were surgical treatment in gynæcology and obstetrics and the role of the pituitary gland in the physiology and pathology of genital organs.

Hypopituitarism (Sheehan's Disease)

Prof. H. L. SHEEHAN showed that, in severe postpartum hypopituitarism, patients who had occasional uterine bleeding had just as great a destruction of the anterior pituitary as those who had permanent amenorrhœa. These atypical patients should not be assumed to have only moderate hypopituitarism, and the entire clinical and biochemical picture must be taken into account in assessing the severity of the condition. Other

speakers emphasised the dangers of sudden stress to those in this subclinical group of hypopituitarism.

R. MURDOCH (Glasgow) reviewed all 55 cases of proved Sheehan's disease admitted to hospital in the Glasgow area in the past 8 years. The interval between obstetric accident and admission to hospital varied from 5 months to 43 years. Most cases were of menopausal age, supporting Sheehan's theory [1] that the latent period often ended at the menopause, possibly when productive ova disappeared from the ovary. Until then the ovaries were capable of secreting some hormone which protected the patient from the effects of deficient function of adrenals and thryoid. Successful pregnancy was the best method of improving the patient's condition, according to Sheehan and Murdoch. Women with hæmorrhage and/or shock at delivery should always be considered potential sufferers from Sheehan's syndrome and should be kept under surveillance for at least a year.

The Vacuum Extractor

J. A. CHALMERS (Worcester) traced the history of the application of traction to the fœtal head by means of a vacuum cup from the work of Yonge [2] in 1705 to the present day. T. G. MALMSTRÖM (Gothenburg) gave a statistical report of his research with the extractor from 1952 to 1960. Since 1958 the extractor had eliminated forceps in cases where extraction by the vaginal route was indicated; and it was particularly valuable in elderly primigravidæ. In Malmström's analysis the vacuum extractor gave better results than forceps in terms of perinatal mortality—31 deaths among 793 forceps extractions (4·1%) and 9 deaths among vacuum-extractor cases (1·5%). E. BRANDSTRUP and P. LANGE (Copenhagen) have routinely used vacuum extraction for instrumental vaginal deliveries in the past year. They found that compared with forceps the vacuum extractor produced less injury, less blood loss, less puerperal pyrexia, and no anæsthetic complications to the mother, and a lower mortality, lower incidence of neonatal asphyxia and cerebral hæmorrhage, though higher incidence of cephalhæmatoma in the infants.

Carcinoma of the Cervix

H. YAGI (Okayama) reported 6 years' experience from 65 hospitals throughout Japan (19,727 patients with carcinoma of the cervix, 55·5% operated upon). A radical operation called "Okabayashi operation" is now widely applied in Japan (complete pelvic lymphadenectomy with extensive hysterectomy). The results showed a stage-I 5-year cure-rate of 85·5% and stage II 64·0%, compared with 71·2% and 14·3% respectively for cases treated by hysterectomy without lymphadenectomy.

DOBROTIN (Gorkij) reported that surgery was being increasingly used in Russia and he mentioned an 82% operability-rate. Since 1949, 1212 Wertheim-type operations had been performed at his clinic, with no fatalities. Local penicillin and streptomycin were applied to the cervix preoperatively to reduce sepsis.

A report by J. T. LOUW (Cape Town) covering the 10 years 1951–60 confirmed that when the lymphatic glands were involved the prognosis in uterine carcinoma (cervix or endometrium) was poor. 201 patients were submitted to Wertheim-type operation 6–8 weeks after radiotherapy. 137 had no gland spread and 100 were alive. 64 had secondary deposits in lymph-glands and only 17 were alive. He questioned the value of lymphatic extirpation and suggested that in patients whose general condition was poor the operation be limited merely to an extended hysterectomy.

F. NOVAK (Ljubljana, Yugoslavia) elaborated his method [3] for prevention of uterovaginal fistula after Wertheim's operation and he also showed an excellent film of the technique (by means of which he has reduced the fistula-rate from 11% to 2%). He emphasised that the utmost care should be taken to protect the terminal part of the ureter, and especially to ensure that it was not allowed to take up a lateral position on the pelvic wall.

J. A. STALLWORTHY (Oxford) described the combined use of radiation and surgery in 203 consecutive operations. The material obtained at operation in the last 110 cases showed residual malignant cells in the uterus in 46%, in the parametrium and vagina in 9%, and pelvic lymph-nodes in 25%. Recent radiobiological research [4] had shown that the probability of a malignant tumour being destroyed by radiation was proportional to the size of the tumour. It seemed logical therefore that the same dose of radiation which might be incapable of destroying cancer cells in glands on the lateral pelvic wall might be adequate to deal with isolated cells in the operative field after lymphadenectomy. For this reason when glands had been found to contain metastatic cancer treatment has been supplemented by radiation to the pelvic walls.

M. A. v. B. BASTIAANSE (The Hague) set out the advantages of surgical treatment, referring particularly to the prevention of local recurrence. He described a technique for the prevention of implantation of metastases both after abdominal and vaginal hysterectomy. Except in very early carcinoma, radium therapy was instituted about four weeks before operation. The vagina was well cleansed preoperatively with gauze impregnated with 60% alcohol, and then tincture of iodine was applied. Both in vaginal and abdominal hysterectomy, a vaginal cuff was dissected out and then carefully closed by interrupted sutures over a gauze impregnated with 96% alcohol. Infection was thus reduced, and loose and superficial cells destroyed.

W. F. BOUWER (Amsterdam), a coworker of Bastiaanse, said that histological examination of operation specimens showed that in more than 10% of cases tumour tissue was found which was radiologically unchanged after the preliminary radium therapy.

H. L. KOTTMEIER (Stockholm) advocated fulguration for the radio-incurable recurrent carcinoma of the cervix. The main complications of this treatment were vesicovaginal and rectovaginal fistulæ.

A. INGELMANN-SUNDBERG (Stockholm) described a special repair method for these fistulæ where muscles from a non-irradiated area were brought as flaps to the site of the fistula. Preferably the gracilis muscle was brought through the obturator foramen into the pelvis.

J. E. AYRE (New York) described a virus manifestation in 0·3% of 50,000 women screened for malignant and premalignant cells of the cervix. Detectable by cytological scrapings, it appeared as a translucent intranuclear or perinuclear fluid zone, transient in duration between infectious stage and premalignancy, and absent in normal cells or full-blown cancers. The halo cells, he said, developed in tissue preconditioned by infection, in an environment of abnormal œstrogenic activity. They appeared to be live cells when examined with other cells of premalignant lesions in fresh unfixed cell-smears using T.M.K. 101 research stain, which revealed pseudopodia and apparent amœboid activity not previously noted in exfoliative cell studies. The usual fate of halo-cell lesions was cancer-in-situ unless arrested by treatment. The suggested sequence of events was that a transmissible agent (viral) was acquired by sexual intercourse. It entered the host cells, and a latent period followed which may last several years. Subsequent changes were conditioned by excess or abnormal œstrogenic activity and related mucus production. Not all women so affected would get cancer unless other determining factors came into play, but without the transmissible agent no cancer would develop.

Thrombosis and Pulmonary Embolism

W. SANDRITTER (Frankfurt) recalled statistics showing that women suffered fatal pulmonary embolism 1·8 times more often than men and that frequency increased with age—72% of all deaths occurring after the age of 50. It had also been shown in Germany that in periods of famine embolism was less common than at other times. Although well-fed and ill-fed patients were equally prone to thrombosis, the thrombi might move more readily in adipose patients (fatal pulmonary

1. Sheehan, H. L. *Proc. R. Soc. Med.* 1961, **54**, 43.
2. Yonge, J. *Phil. Trans.* 1706-7, **25-26** 2387.
3. Novak, F. Modern Trends in Gynæcology and Obstetrics; tome 1, p. 363. Montreal, 1959.
4. Ellis, F. Presidential address, section of radiology, Royal Society of Medicine, November, 1960.

embolism was three times more frequent in overweight patients than in those of normal weight). Weather might also influence the formation and spread of thrombi; embolism was relatively uncommon in the tropics. When the question of the patient's position after operation was raised, Bastiaanse advocated the lateral position.

Hyperemesis Gravidarum

D. V. I. FAIRWEATHER (Newcastle upon Tyne) said that observations on human chorionic gonadotrophin (H.C.G.) excretion in the urine of 90 patients with hyperemesis gravidarum showed that whereas it had previously been thought that H.C.G. levels were high in this disease, excretion was in fact below normal. No correlation was noted between H.C.G. level and outcome or clinical course of the pregnancy.

Conservative Myomectomy

R. B. K. RICKFORD (London) reviewed 178 patients who underwent myomectomy (127 were married). Only 11% were involuntarily infertile. As the usually accepted figure of infertility is about 10%, fibroids seem to be a rare cause of sterility. 110 of the patients were followed for from 5 to 10 years. Only 46·4% of those wished to use the uterus for childbearing, and of these 73·3% were successful. The success-rate in the treatment of sterility by myomectomy was only 15·4%. Cæsarean section in patients who have had myomectomy seemed to be indicated in elderly primigravidæ, in all patients who had had multiple deep myomectomies, when the cavity of the uterus had been opened, or when there was reason to doubt the soundness of the uterine scar. The section should be done before the 38th week, because later the risk of rupture rapidly increased.

A. GIAMPIETRO and R. PARADA (Montevideo) emphasised the value of hysterosalpingography when conservative myomectomy was contemplated, since submucous myomata could then be detected.

Amniotic Infection

B. V. GAVALLAR and D. MERCHAN (Caracas) reviewed the incidence of amniotic infection in necropsy material of 316 stillborn and 209 neonatal deaths (first 24 hours). In the former group the incidence was 36·3% and in the latter 19·1%. The internal organs, umbilicus, umbilical cord, and (in stillborn infants) the placenta and membranes were examined histologically. Fœtal pneumonia was noted in 52 cases (9·5%). Among the factors favouring infection were prolonged gestation, a long labour, and a long interval between artificial rupture of membranes and delivery.

Stress Incontinence of Urine

A. INGELMAN-SUNDBERG (Stockholm) pointed out that the intra-abdominal pressure in normal women was transferred to the same extent to the bladder and to the proximal part of the urethra (i.e., from a functional viewpoint the urethra was intra-abdominal). In women with stress incontinence, insufficient intra-abdominal pressure was transmitted to the urethra. The intravesical pressure would then be higher than the intra-urethral pressure, causing leakage.

In postoperative care after vaginal repair for stress incontinence, E. COPE (Birmingham) advised early mobilisation and physiotherapy. He felt that the use of a vaginal pack and catheter were unnecessary. A local anæsthetic aerosol spray was used to relieve pain and gave good relief in 77% of cases.

Rhesus

M. MAYER (Paris) drew attention to the importance of the examination of the amniotic fluid in deciding whether to terminate pregnancy in cases of rhesus isoimmunisation. Spectrophotometric analysis of the fluid would detect the presence of bilirubin, and this was a better guide to the severity of immunisation than the study of maternal antibodies.

Commenting on the use of pitocin induction of labour in hæmolytic disease of the newborn, A. H. C. WALKER (Manchester) based his policy for time of induction on antenatal liquor tests (parencentesis at 32 weeks) supported by antibody titres. Fœtal survival was now 80% compared with 66% before such methods were adopted in that unit.

Toxæmia of Pregnancy

A. DARRAGH and C. CUSSEN (Dublin) put forward new ideas about the ætiology of toxæmia of pregnancy. An inadequate response of the zone glomerulosa of the adrenal cortex to the stimulus of an elevated serum-progesterone level seemed to be the primary defect. Diminished secretion of aldosterone resulted in hyperactivity of the renal juxtaglomerular apparatus with increased secretion of renin and hyperplasia of glomerular cellular elements. The decreased secretion of aldosterone, a much raised intracellular sodium content, and a pathognomic lesion of the renal glomerulus formed an endocrine, electrolytic, and histopathological triad which was a consistent feature of established toxæmia of pregnancy manifested clinically by œdema, hypertension, and albuminuria.

Anæsthesia for Operative Obstetrics

W. D. WYLIE (London) concluded that local analgesia was much to be preferred in obstetrics for reasons of both maternal and fœtal safety. Pudendal nerve block was suitable for a high proportion of vaginal operative procedures and could be conveniently and simply carried out by the obstetrician. The safety of general anæsthesia depended more on the experience and skill of the anæsthetist than on a particular drug or technique. The use of a muscle relaxant with an endotracheal tube and very light anæsthesia had material advantages, particularly when the infant was at risk.

Induction of Labour with Oxytocin

W. C. W. NIXON and D. G. BONHAM (London) condemned the ritual of oil, bath, and enema for induction of labour, saying " it should be reserved for those women on whom the obstetrician wishes to inflict some form of sadistic punishment ". They reviewed 152 cases who received oxytocin (' Syntocinon ') infusions. In the last 12 months reviewed, the usual routine was modified and oxytocin was given by a slow injection apparatus (instead of a drip). The main indications for induction were toxæmia (35%) and spontaneous rupture of the membranes without labour (20%). The oxytocin sensitivity test [5] was employed, low amniotomy was performed, and should the cervix not be favourable, the indications for induction were reassessed. If induction still seemed urgent a " ripening " infusion was started. Penicillin and streptomycin were given after 20 hours (when a cervical swab was taken for bacteriological examination). Infusions were stopped overnight if the cervix was not dilating after 12 hours. Normally infusion was continued until 30 minutes after the delivery of the placenta. Ergometrine (0·5 mg. intravenously) was given with crowning of the head. With the adoption of the pump method of infusion the failure-rate has fallen from 34% to 10% and the mean amniotomy-delivery interval from 55 to 42 hours.

D. C. A. BEVIS (Manchester) did not feel that previous cæsarean section was a contraindication to oxytocin induction, and he quoted 41 cases in which it had been used, 1 resulting in rupture of the uterus.

RHEUMATISM

FROM A CORRESPONDENT

THE 10th Congress of the International League Against Rheumatism was held in Rome on Sept. 3–7. Papers dealt with almost every aspect of rheumatism and connective tissue, and, not surprisingly, a remarkable number were concerned with immunology and the immunological aspects of rheumatic diseases.

Rheumatic Fever

Among the many interesting papers on rheumatic fever was one by M. SPAGNUOLO and A. R. FEINSTEIN on the experimental reactivation of subsiding rheumatic fever. Their data were consistent with the hypothesis that most attacks of rheumatic fever created a fixed amount of inflammation which appeared and dispersed in a finite length of time, and the post-therapeutic

5. Smyth, C. N. *Proc. R. Soc. Med.* 1958, **48**, 677.

rebound represented the reappearance of inflammation that had accumulated under suppressive treatment. Increased tolerance of heparin has previously been reported both here and in France, and this was confirmed by V. P. KAZNACHEYEV in the U.S.S.R., who regarded it as a test of considerable diagnostic value. Several workers reported favourably on the prophylaxis of the disease by various antistreptococcal agents, and this must now be accepted as an outstanding achievement in the control of the disease. The vexed question of the nature of the Aschoff body and of the myocardial origin of its characteristic giant cells was again aired by G. E. MURPHY.

Of outstanding importance was the review by E. F. BLAND of the 382 cases of so-called " pure chorea " seen at the Home of the Good Samaritan, Boston, since 1921. The striking absence of cardiac involvement at the time of their active illness contrasted with the insidious appearance of mitral stenosis in a considerable number during the ensuing 10 to 20 years.

Some light was thrown by A. TARANTA and his colleagues on the problem of the genetic basis of rheumatic fever by a study of the incidence of the disease in monozygotic and dizygotic twins. Although their material was numerically inadequate to justify firm conclusions, their findings were consistent with the view that genetic factors do play a role in the ætiology of rheumatic fever. But, since less than a fifth of the monozygotic twins was concordant, these factors were presumably subordinate to those of the environment.

Without question the most exciting contribution to the problem of rheumatic fever was the claim put forward by G. D. ZALESSKI and R. S. DREISEN (Moscow) to have isolated a virus from patients with rheumatic fever and to have produced with it a similar disease in rabbits. The virus was claimed to be distinct from Coxsackie, poliomyelitis, influenza, Echo, and other viruses. As a similar claim was made by Zalesski in 1959 at the 4th European Rheumatological Congress, it is disappointing that no-one has yet confirmed or repudiated these remarkable findings.

Rheumatoid Arthritis

Amongst many contributions dealing with the distribution of the rheumatoid factor in patients with rheumatoid arthritis were two of special interest because of their suggestion of a pathogenic role for the factor. The first, by A. E. FINKELSTEIN et al., showed a correlation between the phenomenon of sludging of the blood in vivo and the latex agglutination titre; and the second, by V. BIANCHI, drew attention to the agglutination of the platelets when cooled to 5°C in rheumatoid plasma. Such an agglutination might well underlie the Raynaud phenomenon sometimes shown by those patients.

A study of the relatives of patients with Still's disease, by B. M. ANSELL, E. G. L. BYWATERS, and J. S. LAWRENCE, revealed strong evidence of the importance of genetic factors in this disease. At least two genetic factors seemed to be involved; one associated with spondylitis and the other with sero-negative polyarthritis. In view of the obvious significance of heredity in the ætiology of rheumatoid disease H. BARTFIELD undertook a comparative study of the chromosomes in tissue cultures of leucocytes of patients and normal subjects. No difference was detected in chromosome number or morphology.

Related Diseases

The well-known correlation between rheumatoid arthritis and psoriasis was further substantiated by J. M. POAL and J. A SARRO (Barcelona), who found the two diseases coexisting ten times as often as would be expected by chance. In agreement with other workers they found that in these patients with psoriatic arthritis the Rose test was consistently negative.

The relationship between discoid and systemic lupus erythematosus is far from clear. J. C. BENNETT and his colleagues in Birmingham, Alabama, reported the results of clinical and pathological investigations on a series of 17 patients with discoid lupus. Only 3 gave consistently negative results with all their immunological tests, from which they concluded that many patients with longstanding lupus have subtle immunological manifestations usually found in the systemic form of the disease.

Several papers were concerned with the clinical overlap of the various kinds of collagen diseases. Such overlap was especially well shown in a family study of progressive systemic sclerosis by W. G. ROBBINS et al. (New York). In this study rheumatoid arthritis was found in a significantly increased incidence amongst the relatives, and rheumatoid and antinuclear factors were commonly found in the sera of the patients themselves. Similarly the simultaneous occurrence of the classical features of rheumatoid arthritis and disseminated lupus were described in 6 patients by M. SILVER et al. (New York). They pertinently asked, " Are these overlap syndromes really a pathologic state wherein two or more connective-tissue disorders coexist . . . or may the rheumatic component of systemic lupus be indistinguishable at times from late rheumatoid arthritis ? "

Gout

Recent advances in knowledge of the metabolism of purines and the introduction of potent uricosuric agents have greatly stimulated interest in gout, and about 50 papers were concerned with its nature and treatment. The long-term uricosuric treatment of 64 patients with gout at Ann Arbor, Michigan, was described by G. R. THOMPSON and his colleagues, and they concluded that, with the available therapeutic agents, " in all but a very few patients, it is now possible to completely control gout—the acute attacks, chronic symptoms, and tophus formation ". This optimistic conclusion was shared by almost all the other contributors to the subject. T. G. BENEDEK, however, drew attention to the anti-uricosuric effect of salicylate and emphasised that aspirin, commonly used without medical direction, could within a few days overcome the effects for which probenecid, sulfinpyrazone, or zoxazolamine had been prescribed. Some interesting and unexpected results were presented by S. COBB and his associates at Pittsburg on the distribution of serum-uric-acid values in various industrial populations. The incidence of levels above 6 mg. per 100 ml. was much higher in executives than in craftsmen, and significantly high values were also found in PH.D. scientists. A correlation between the incidence of gout in a population and the frequency of raised levels of serum-uric-acid was well illustrated by J. L. DECKER and his colleagues at Seattle in a comparative study of these parameters in Filipino workmen and a control group of normal white prison inmates.

Immunology

Several of the most interesting papers were presented at a single session devoted to immunology. J. ROTSTEIN and R. A. GOOD drew attention to the extraordinarily high incidence of connective-tissue disease in their series of patients with agammaglobulinæmia, but their conclusion that this was evidence for an infectious ætiology was unconvincing. C. STEFFEN (Vienna) gave the results of his Coombs consumption test on the sera of patients with rheumatoid arthritis. These results suggested the presence in rheumatoid sera of an autoantibody to some connective-tissue component. The immunofluorescent technique was used by E. HESS and M. ZIFF in a fairly extensive attempt to detect evidence of autoimmune reactions in rheumatic fever, rheumatoid arthritis, and ulcerative colitis. Slides were shown of some of their positive findings.

Rheumatoid Factor

Much of the symposium and many papers at other sessions were devoted to the rheumatoid factor. An excellent account of his work on the Gm groups was given by MORTEN HARBOE (Oslo); he showed clearly that the rheumatoid factor consisted of a whole group of closely related but nevertheless separate macroglobulins. A similar conclusion was reached by V. P. BUTLER and J. H. VAUGHAN as a result of an extensive investigation in which γ-globulin was attached to red cells by covalent linkage via diazotised benzidine. By this method the differences between individual human γ-globulins, as well as differences between those of different species to act as reactant, were clearly revealed.

The immunological status of the rheumatoid factor is still sub judice, but the majority opinion regarded it as an antibody against γ-globulin of the 7S variety. The main unsolved

problem is whether the antigen is native 7S γ-globulin or whether it must have first undergone some change in configuration. The paper by J. ORESKES, J. M. SINGER, and C. M. PLOTZ on studies of human γ-globulin reactivity with rheumatoid-arthritis sera provided evidence for the second alternative. They showed, for example, that the known facts of the interaction of rheumatoid factor with aggregated γ-globulin were not readily attributable to aggregation alone, but suggested the possibility that the increased reactivity induced by heat was due to denaturation of the 7S molecules.

GERIATRICS

FROM A CORRESPONDENT

THE European clinical section of the International Association of Gerontology held its third meeting at The Hague on Sept. 13–16 under the presidency of Prof. L. VAN DER HORST. The first meeting of the section in 1958 attracted only about 100 participants: this time there were over 400, representing twenty countries. The main themes of the conference were the geriatric aspects of mental disorder, blood formation, and malignant disease. Adaptation to retirement, nutrition in the elderly, and sexual problems were also discussed.

Geriatrics provides a meeting-ground for physicians and psychiatrists, and it was significant that the first paper of the meeting by O. DEMOL (Belgium) was devoted to the pathogenesis of mental disorder in the elderly, emphasising the physical as well as the social and psychological aspects; and he was followed by R. A. ROBINSON (Scotland) with a description of a special unit for geriatric psychiatry.

Among many papers on psychotropic drugs, F. POST (England) described the value of phenothiazine tranquillisers for elderly schizophrenics.

O. EICHHORN (Austria) described an isotope technique for assessing the cerebral circulation and concluded that this was abnormal in almost all elderly patients with mental disorder.

J. A. HUET (France) showed that the care of the mentally infirm could not, for humane as well as for economic reasons, be provided by an unlimited increase in hospital accommodation, and the problem was being tackled in Paris by other means. M. L. INSLEY and J. D. B. ANDREWS (Wales) presented an important assessment of the problem of the ambulant confused patient and suggested that this problem was smaller than was commonly supposed and could be solved by providing a comparatively small number of hostels, of a homely kind and not necessarily within the hospital service.

P. SAINSBURY (England), discussing suicide in later life, emphasised its relation to physical illness, its greater incidence in men, and the unimportance of the economic factor. Prevention probably lay in changing our social climate to give an increased significance to old age. E. DRIETOMSZKY (Hungary) claimed that a good education was the best preserver of mental activity in patients over 100.

D. A. WEBSTER, W. MACKENZIE, and E. WOODFORD WILLIAMS (England) described a study of the life of the red cell in old age. They found that it was normal, and E. UNDRITZ (Switzerland) also confirmed that red cells in old age were indistinguishable from those of young subjects. In white cells, on the other hand, old-age changes were described by S. DENES (Hungary) and G. BRUSCHKE and F. H. SCHULTZ (Germany).

Discussing the susceptibility to cancer at various ages R. DOLL (England) said the reasons for the increase of incidence with age were still obscure. H. DE JAGER (Netherlands) drew attention to our ignorance of the natural history of malignant disease in old age: its course was very variable and this made assessment of treatment unusually difficult. S. J. FIRTH (England) showed that cancer of the lung and other sites was often incidental, and not the main cause of death, though common in old age. R. HERBEUVAL (France), the chairman of the clinical section, described important work on the recovery of cancer cells from the blood by a method of leucocyte concentration. Such cells were most readily demonstrated in lymphosarcoma and reticulosarcoma, and more rarely in growths of the alimentary tract where they were held up in the liver and the lung.

F. H. SCHULTZ and D. SCHMIDT (Germany) believed that most old people were short of vitamins and that the serum protein and iron levels could be raised by giving vitamins.

S. BRAADBAART (Netherlands) gave an account of the previous sexual habits of a group of elderly men in a welfare home: the average age at which coitus ceased to take place was 68 for married men and 58 for bachelors.

The meeting ended with a discussion of future prospects for geriatrics by R. J. VAN ZONNEFELD and J. TH. R. SCHREUDER (Netherlands), who were the principal medical organisers of this very successful meeting.

Geriatrics is getting a great deal of attention in the Netherlands, and Zonnestraal Hospital, near Hilversum, which conference members visited, showed what one kind of geriatric hospital may look like in the future. The hospital, a converted sanatorium, had a fine sense of space, adequate day-rooms, with chairs round small tables like a Continental cafe, small wards, none containing more than 8 beds, with a hanging cupboard for every patient, and an elaborately equipped physiotherapy department. The most original feature was a class for aphasic patients, in which it was demonstrated that some aphasics, like some stammerers, can still sing when they can no longer talk.

Personal Papers

PSYCHOLOGICAL EFFECTS OF HÆMOPHILIA

MY only qualification to write on this subject is 30 years' first-hand experience of hæmophilia; and even this is a doubtful recommendation, for my views will be regarded as subjective (which they are, of course) and therefore suspect. I must also admit that it is a qualification that I would willingly forgo. Apart from other considerations, the appellation "bleeder", though medically correct, is horribly inelegant.

First among the effects of hæmophilia I would place mental stress. The inconsistent nature of the disease demands continual mental readjustment. At times you are comparatively fit, at others you cannot sit up in bed without help. The effect on education and employment can readily be imagined. It is pure chance how many early years are spent in sickroom or schoolroom. In later years a reputation for unreliability too often hinders promotion, and to retain even the humblest job becomes an achievement.

Admittedly everyone who is disabled faces problems of this kind. It is the unending and unpredictable variation in degree of disability that is peculiar to the hæmophiliac. Uncertainty is mentally tiring, and nothing is less certain than the course of the hæmophiliac's life. He can, for instance, never confidently book ahead for holiday or theatre. To quibble at inconvenience, when so many people can never enjoy such pleasures, may appear to argue a lack of proportion but it would, of course, be wrong to reject normal life because every plan or arrangement carries the likelihood of last-minute disappointment.

This inconsistency brings other social problems. Most people readily make allowances for an obvious and permanent disability; but who can blame them if they are foxed by the hæmophiliac? Yesterday they saw him apparently fit and well; today he refuses some engagement on the plea of illness. Perhaps tomorrow they see him again in apparent good health. They not unreasonably

conclude that he was using a conventional method of escaping an unwelcome invitation. It is difficult to explain such lapses convincingly, especially when they are likely to recur often.

His family and close friends inevitably share these uncertainties and disappointments. Perhaps their lot is even harder than that of the hæmophiliac himself, for it cannot be pleasant never to know in what state of health your partner, husband, brother, or son may arrive home.

And their patience may be tried in other ways. The hæmophiliac has so many warning twinges that he cannot mention them all. If he did, he would soon begin to sound like a querulous hypochondriac. Now and again a threatening hæmorrhage does not develop and all is well. Often the probability of illness hangs over his head for days, and then the struggle to continue with work and other commitments becomes an almost intolerable strain. Conventional politenesses and conversation become at best an act and at worst an impossibility. In the doctor's consulting-room, too, the hæmophiliac may seem over-apprehensive; but so much harm can be done to him so quickly during medical examination, even by skilled and careful hands, that he is grateful when his warnings are respected.

Of course, for a lazy person such as myself, hæmophilia offers some compensations. From the depths of my deck-chair I can reflect on the success I would have made of life " had I been fit ". I remember a perspiring cousin offering to swap the privilege of mowing the lawn for ". . . your bloody hæmophilia for half an hour." The mental approach shown by this remark is correct, for the hæmophiliac hates fuss and solicitude. He must be allowed to make his own decisions and, if he wishes, to take some risks. He is forced to surrender so much of his personality by his dependence on others that he must retain as much freedom of decision as possible, though this sometimes may make him appear impatient and intolerant of argument.

Between bouts of illness past discomforts are forgotten to a surprising extent, and there is a compensating pleasure in the utter delight of feeling well. But although I try not to worry about the next episode, and to live as normally as possible, I always know that it is inevitable and that " awareness " and care and calculation are necessary. This is not a morbid preoccupation engendered by self-pity. If the hæmophiliac does not guard against overexertion or strain, he will suffer for it. This continuous need for calculation is his greatest handicap. His mind is always partly preoccupied in assessing the possible consequence of any action—so much exertion or movement and no more. The situation is further complicated because the amount of activity possible without ill-effect varies from day to day. This variation, which is often without apparent reason, turns life into a guessing game, where the penalties for guessing wrongly can sometimes be severe.

It needs a moderate amount of will-power and restraint to give up a simple enjoyment merely because of the possibility that it *may* provoke a hæmorrhage. And, having done so, you are seldom certain that the sacrifice was necessary. This everlasting preoccupation becomes so normal that it is hard to picture life without it and to realise that it is not universal. How difficult it must be, then, for others to appreciate the hæmophiliac's approach to life.

I have accordingly written this, not as a chronicle of complaints, but as an explanation of special difficulties, and I hope that it will be accepted as such.

The Widdicombe File

LXIX.—A VIRUS LAB?

MY DEAR WHIDDON,

The physicians, as you know, have been asking for a virological laboratory for a long time; and if we have not given the matter much thought it is because we all knew the till was empty. The Regional Hospital Board has now mentioned that it has a few thousand spare sovereigns in the cupboard which are available for any reasonable project. We shall have to decide (pretty quickly) whether a virological laboratory is likely to be more useful to the hospital—i.e., to its patients—than the rather grandiose plans for the departments of psychiatry and physical medicine. I very much hope that you will attend the meeting next Tuesday to give us the benefit of an uncommitted opinion.

A " virus infection " is now the fashionable label for any febrile illness N.Y.D. (I gather that the stars of stage, screen, and politics suffer from nothing else). It is at least as accurate as " deep-seated mischief " or " a gastro-pulmonary state of affairs ". In fact the virologists can provide evidence for the specific diagnosis of quite a number of diseases which have hitherto been diagnosed on trust, and besides this have identified many new agents some of which are almost certainly the cause of human disease. Some of their diagnoses are of real value either as a guide to treatment or prognosis or because they exclude some other possibility. But the factor which limits their usefulness so much is the time taken by the technical processes in the laboratory. *Bis dat qui cito dat* is as true in medicine as anywhere. It is true that a few viruses can be recognised immediately under the microscope, but the others—if they can be isolated at all—must be grown in tissue culture or in some animal; and if you can get an answer from these under five days you are fortunate. Alternatively, the diagnosis can be made on the indirect evidence of the antibodies in the patient's blood; but you will, of course, have to wait for the patient to produce his antibodies. To make a confident diagnosis most virologists—they are modest and careful men—prefer to examine two specimens of serum one taken early in the disease and another some 14 days later. By the time the doctor learns that his patient's " cold " was due to Sendai virus he will have forgotten his name.

We who work at the laboratory bench have always had difficulty in distinguishing what is useful in clinical practice from what is merely interesting. (If the distinction were easier there might be fewer papers to read.) How often are the findings of the virological laboratory of value in the diagnosis and treatment of disease? Now that the elder brethren are no longer with us, I would always be grateful to any virologist who would confirm or deny the diagnosis of smallpox immediately and convincingly. If it is not smallpox it is chickenpox. Only a very experienced practitioner would admit that he needed anyone's help in diagnosing measles. Some experience in rustic practice and the history of disease in an animal are usually enough to identify cowpox and orf (or lure as they call it hereabouts). For the recognition of herpes simplex or zoster most of us are content to rely on our native senses. The loudest advocate of a virological laboratory is our pneumatic colleague who harbours a

burning interest in the " atypical pneumonias ". Retrospectively it is interesting to know that the disease was, in fact, psittacosis or Q fever; but I doubt whether either diagnosis influences his treatment. Similarly the infections of the upper respiratory tract, whether due to an influenza or an adenovirus, have been cured by bed and aspirin before the laboratory report arrives.

When there is an epidemic, I agree, retrospective diagnosis of the first few cases is of more value than it is in isolated infections. For the same reason it's worth making a specific rather than a presumptive diagnosis in any patient suspected of having poliomyelitis. There are several other enteroviruses which give rise to similar but on the whole less severe diseases, and if we can exclude the presence of poliovirus we relieve both individual and public anxiety. I think the laboratory is even more useful in the investigation of aseptic meningitis and encephalitis. The antibodies to the virus which causes lymphocytic choriomeningitis seem to appear early in the disease, and when these are found in combination with a typical history and cerebrospinal fluid, I am prepared to swear my davy on the diagnosis to the exclusion of tuberculosis or anything else. The specific diagnosis of mumps encephalitis is almost as valuable: it may not alter the treatment but it gives a very fair prognosis. And that's about all. I have said nothing of the epidemiological studies which involve a virological laboratory: they are fascinating but they are not the function of a general hospital.

You may ask if the virologist is likely to make quicker and more useful diagnoses in time to come. I wouldn't care to guess. In 1880 Koch was working with crude and unhandy fluid and gelatin culture media, but his bacteria grew about as quickly as ours do. It may be that new tissue cultures or untried animals will be found which will persuade viruses to grow as quickly as bacteria, but it is equally possible that they are now near their reproductive maximum. I don't know whether electron microscopy is in its infancy or near finality—or whether it is ever likely to be a diagnostic tool. Infra-red spectroscopy has possibilities. It may even be possible for the biochemist to name a viral cell by its specific components. None of these possibilities—and there are many more—need influence us on Tuesday.

Judging by what I hear, a virological laboratory in a general hospital with 400 beds is likely to receive about 500 specimens per annum, of which 10% will give some sort of positive answer. General practitioners will send very few. In other words the virologist wouldn't be the busiest member of our staff, but if he has any imagination he will not be bored. I used the analogy of Koch before, and I think it holds good here. 1880–1900 was the golden age of bacteriology, and I suspect that a future generation of virologists will use the same term of the present era. Koch and his contemporaries spent a lot of time trying to define clinical entities in terms of a specific cause. The virologist today faces a similar problem vice versa: he can identify the specific causes but has not yet defined them in terms of clinical medicine—or not much. School epidemics due to an adenovirus must often have been labelled flu until one observant eye noticed that the disease has an incubation period of about 5 days and is followed by no period of depression. This is the kind of work which is done best by the man who works next door to the wards. I wouldn't wish to put such a scheme before our committee—research is a word that they distrust—and we shouldn't be justified in taking the Board's money if research were the main purpose of this laboratory; but if our virologist didn't do some original work I would be disappointed.

We shall, I'm afraid, have to talk about the *cost* of the proposed laboratory—and it will be quite a lot; not only in bricks and plate glass and stainless steel but also in wages. (A virological laboratory uses more staff per specimen than any other hospital laboratory.) For this we shall get no more than a pint-size laboratory. Now within this Region—and in fact less than 60 miles away—there is already a virological laboratory which handles several thousand specimens every year, and nothing would please its director more than to add ours to his total. Is he empire-building? Probably—but that's a disorder of personality that doesn't worry me as long as our specimens are examined satisfactorily. If a laboratory of our own were likely to give us quick answers, I think we should have our own virologist. If there is to be an inescapable delay of at least 5 days the addition of a few hours in transit will be negligible.

There is another more technical argument for centralising this work. We learned long ago that in doing such a test as the Wassermann there's a minimum number below which accuracy suffers for want of internal controls. I have no doubt that the same is true of much diagnostic virology: the laboratory with more specimens and more experience will do the better work. The upper limit is reached when the staff forget that their raw material is something more important than a row of numbers in a book—and the same limit holds good for every part of the N.H.S. It would be more convenient to all of us to have our tame virologist on the spot, but a communion of ideas over a span of 60 miles is not impossible. You accept without question that your patients have to be sent elsewhere for radiotherapy: do you find it difficult to keep in touch with the radiotherapist?

More pathology of all sorts is delegated to experts than most people know. I can't identify the more exotic salmonellas, nor can our biochemist estimate 17-ketosteroids. It's part of a tendency which touches almost every department of the hospital. Central sterile supply has come to stay: how large an area can be served efficiently and economically we must learn the hard way. I am told that every argument used for C.S.S. can be applied to hospital laundering. We already have central purchasing and if this sometimes drives you to blasphemy the fault lies not with the principle but with the local practice (and your handwriting). A small hospital such as ours doesn't expect to have a chest surgeon on the staff. On the whole it is easier to move patients than doctors, nurses, and impedimenta; and, though some of our ambulances are almost primeval, a journey is often less dangerous to a patient than a lack of specialised skill in his attendants. And so on.

Our main difficulty in planning the development of the health sevices is that no-one has yet done the operational research which might give us some guidance on the right size of things—or if they have the results have not come to Widdicombe. Our hospitals were sited at the time when the journey to Exeter took most of the day in the carrier's cart: if you take more than 40 minutes you think your Jaguar has a spavin. The south of England is littered with hospitals of 10–200 beds, unsuitable for specialist services, difficult to staff, and expensive to run. The motor ambulance—and soon, I hope, the helicopter—has

changed the map. I have little doubt that in times to come our successors will have fewer, bigger, and better hospitals—and each will have its own virological laboratory.

I shall vote against this proposal—reluctantly. In 5 years' time I may well take the other side.

Yours sincerely,

HARRY HAWKE.

Before Our Time

HUMAN ORIGINS

Recent Discoveries at Olduvai Gorge

LESS than two years have passed since Dr. L. S. B. Leakey, of the Coryndon Museum, Nairobi, announced the first of a series of remarkable discoveries at Olduvai Gorge, Tanganyika, but these have already begun to revolutionise our thinking on human origins.

In July, 1959, Dr. and Mrs. Leakey discovered a hominid skull which was lying partly exposed on the slopes, 22 ft. below the upper limit of Bed I, the lowest stratum of the Pleistocene sequence at Olduvai. Excavation of the site revealed that the skull was fragmented but almost complete. It was lying on a living-floor with tools of a recognised culture (Oldowan) as well as waste flakes and unworked stones foreign to the site; in addition there were some broken and splintered bones of small animals which had apparently been part of the diet of the incumbents. Subsequently, a tibia and fibula were recovered from the same living-floor. Dr. Leakey named the skull *Zinjanthropus boisei*.

Last year, excavations were started at a slightly lower level of Bed I, and in December Dr. Leakey reported the discovery of a number of adult and juvenile bones of the hand and foot, two clavicles and some skull fragments, all clearly hominid. This was rapidly followed by the important discovery of a juvenile mandible from the same level. A number of stone artefacts of an Oldowan culture have also been found on the juvenile site.

At this time excavation was being carried out in Bed II at a stratigraphic horizon which had previously yielded large quantities of stone tools of a fairly advanced Chellean culture (Chellean 3). In December at this horizon an incomplete cranium was discovered of a hominid form dating to a much more recent geological age than *Zinjanthropus*. Dr. Leakey unhesitatingly placed this individual in the genus *Homo* by naming it " Chellean " man.

Thus, in a remarkably short time, the promise of Olduvai Gorge had been fulfilled. The great importance of this region as a palæontological hunting ground has been appreciated since 1911, when a German entomologist picked up a number of fossil bones which had been eroded on to the surface of the slopes of this East African Pleistocene canyon. Since 1931 Dr. Leakey has made repeated visits to the gorge where he has been steadily building up the evidence of an early stone-age cultural sequence. The picture of Olduvai as an important centre of human evolution lacked only the evidence of the toolmakers themselves; until the discovery of " Chellean " man, no hominid remains, other than two teeth, had been discovered in association with this well-recognised early stone-age industry. Now, not only is the maker of Chellean tools known but his cultural predecessors, the fabricators of the Oldowan pebble tools, have probably been discovered.

THE SEQUENCE?

With only preliminary reports on the fossil bones it is impossible to say precisely where these East African hominids fit into the human evolutionary sequence. Most palæoanthropologists agree that hominid evolution in the Pleistocene consists of three stages—the *Australopithecus* stage, the *Pithecanthropus* stage, and the stage of *Homo* (true man). The three stages are morphologically continuous. Estimates of cranial capacity, for instance, show a serial increase from 450–550 c.cm. for *Australopithecus*, 775–900 c.cm. for *Pithecanthropus erectus erectus* (Java man), and 1000–1300 c.cm. for *Pithecanthropus erectus pekinensis* (Pekin man) and 1100–1500 c.cm. for *Homo*. Chronologically, however, it has always been believed that the first two stages overlapped in the lower middle Pleistocene and that therefore the *Pithecanthropus* group and the *Australopithecus* group could not have formed an ancestor-descendant series. This view may need to be modified in view of the revised dating of the volcanic rocks of Bed I at Olduvai by the potassium-argon method (recently announced by Leakey, Evernden, and Curtis [1]), and of the basalt layer underlying Bed I, by Gentner and Lippolt of Heidelberg University, announced at the recent British Association meeting, but yet to be published. The two sets of results are somewhat contradictory; but, whatever the final conclusion, it is highly likely that the South African australopithecines will have to be backdated to perhaps as much as 900,000–1,000,000 years ago. This being so, the chronological overlap between *Australopithecus* and *Pithecanthropus* may largely disappear.

How then may the Olduvai fossil discoveries fit into, or modify, this sequence of *Australopithecus-Pithecanthropus-Homo*?

The discovery by Professor Arambourg in 1954 of *Atlanthropus*, at Ternifine in Algeria, strongly suggested that the pithecanthropine stage of human evolution was worldwide and not merely a local development in the Far East as had at one time been thought. " Chellean " man may well be, therefore, an East African representative of this stage; certainly a simple inspection of the skull indicates a number of resemblances to *Pithecanthropus*, including the prominent supraorbital ridges and the rather flattened vault. Dr. Leakey believes, on the other hand, that the resemblances of the " Chellean " skull to the pithecanthropines are " superficial " and that the new skull shows many points of similarity with the Steinheim skull, which is, of course, regarded as of the genus *Homo*. Certain resemblances, too, have been noted with the African neanderthaloid forms (Rhodesian man and Saldanha man). The skull in its admixture of characters appears to offer support to those of us who hold that the middle Pleistocene hominids, largely isolated by geographical and climatic conditions, evolved to form a " spectrum " of varieties (as Dr. J. S. Weiner has put it) from which the later *sapiens*, Neanderthal, and neanderthaloid groups (including Rhodesian man) arose. It seems likely therefore that when the " Chellean " skull has been fully studied it will help to close the gap between the latter two stages of human evolution.

ZINJANTHROPUS

The position of *Zinjanthropus* from Bed I is perhaps a simpler problem in that it appears to be—and here most

1. *Nature, Lond.* July 29, 1961.

authorities agree—an australopithecine. Its affinities are with *Paranthropus*, the large clumsy, vegetarian form whose remains are known at Swartkrans and Kromdraai in South Africa, rather than with the more lightly-built carnivorous *Australopithecus*. The new potassium-argon dating of volcanic tuffs at the *Zinjanthropus* level suggest that the Olduvai australopithecines were considerably older than either the South African representatives or the australopithecine fragments of the Jordan valley. Recent discoveries in the Lake Chad area by French palæoanthropologists in Lower Villafranchian deposits indicate that the australopithecine stage of human evolution was widespread both in space and time.

The existence of a *Paranthropus*-like form at Olduvai and later at Swartkrans and Kromdraai in South Africa seem to suggest that this genus, whose morphology is indicative of recent forest-dwelling, was moving out peripherally from a central African habitat. The fossil record in South Africa indicates that *Australopithecus*—and of the two australopithecine genera *Australopithecus* appears to be the better adapted for living on the plains—was already in possession of the Sterkfontein valley when the *Paranthropus* group moved in. The first evidence of *Paranthropus* in South Africa coincided, according to Dr. C. K. Brain, with some alleviation of the arid nature of the climate. Dr. J. T. Robinson believes that the two australopithecine genera, having different ecological requirements, could have successfully occupied the same territory.

When the association of *Zinjanthropus* with a living-floor containing worked stones was announced, it was concluded that the problem whether australopithecines were or were not toolmakers was finally solved. But doubt remains in some quarters. Dr. Leakey's discovery of what he believes to be a more advanced hominid than *Zinjanthropus* at a lower level in Bed I has no doubt contributed to this caution; for *Zinjanthropus* may have been the victim of the more advanced form—the hunter's prey rather than the hunter himself. It is increasingly apparent that the empirical definition of man as "man the toolmaker"—a concept so largely sponsored by Dr. K. P. Oakley—must be based on morphological considerations such as the form and structure of the hand as well as on the circumstantial evidence of association.

THE PRE-ZINJANTHROPUS JUVENILE

The third of Dr. Leakey's recent discoveries at Olduvai Gorge—the pre-*Zinjanthropus* juvenile at a lower level of Bed I—is at present the most problematical. The parietal bones suggest to Dr. Leakey a cranial capacity greater than that of *Zinjanthropus*, indeed of any known australopithecine; he also believes that the teeth, particularly the lower premolars which elongate from front to back and narrow from side to side, cannot be matched among the South African fossils. Provisionally he is inclined to look upon the pre-*Zinjanthropus* juvenile as somewhat closer to true ancestors of *Homo* than are the australopithecine group.

What makes this discovery particularly interesting is that a number of adult and juvenile limb-bones were also recovered from the site, including a remarkably complete foot and a number of carpal and phalangeal bones of the hand. Such bones—rare in human palæontology—are of considerable importance, for they should provide information impossible to obtain from skulls and teeth, about the way of life of these forms, the extent to which they were bipedal, and their capacity for tool-using and toolmaking.

A MAJOR CONTRIBUTION

The revision of Pleistocene dating suggested by Leakey, Evernden, and Curtis which places the *Zinjanthropus* level at 1·7 million B.P. instead of 600,000 B.P. would be welcomed by anatomists and anthropologists, who have always been concerned at the short time available in which to accommodate remarkable changes necessary to convert an ape-man into a true man. However, in view of the uncertainty created by the announcement of the contradictory results of Gentner and Lippolt, it is probably wiser for the time being, to avoid revision of present theories to fit the new Pleistocene time-scale.

The discoveries at Olduvai Gorge during the past two years will, no doubt, be judged in the future as a major contribution to human palæoanthropology, ranking with Dubois' discovery of Java man and Dart's recognition of the adolescent australopithecine at Taung. Unquestionably there are human relics still to be found at Olduvai, at both higher and lower geological levels than those already known. There is still much to be done in the field and in the laboratory before the history of Pleistocene man in Africa can be written.

JOHN NAPIER

Medicine and the Law

The Human Tissue Act

THE Human Tissue Act came into operation on Sept. 27. The main object of the Act is to make it clear that under certain conditions parts of a human body may lawfully be removed after death by a registered medical practitioner and used for therapeutic purposes, medical education, or research. The conditions relate mainly to the giving of the necessary authority, and these have been framed with scrupulous—some may think overscrupulous—regard for the susceptibilities of relatives. Authority can be given only by the person lawfully in possession of the body. Where the deceased died in hospital, this will be the management committee or board of governors until the executors or relatives claim the body. Where the deceased died elsewhere, the question what person is lawfully in possession of the body is one of fact; thus it may be the husband in the case of a deceased wife, parent in the case of a child, the executor (if any), or even the householder in whose premises the body lies. Undertakers are precluded from giving authority.

Where the deceased has made a request in writing or orally in the presence of two witnesses during his last illness, the person lawfully in possession of the body *may* (but is not required to) give the necessary authority. The request and the authority may be limited to a specific part of the body and/or a specific purpose. Where the deceased has not made any request, the person lawfully in possession may give authority if, having made such reasonable inquiry as may be practicable, he has no reason to believe that the deceased in his lifetime had expressed any objection or that the surviving spouse or any surviving relative objects. It seems unfortunate that the word "relative" is not defined in the Act; the Minister of Health has expressed the opinion that it should be interpreted in the widest sense to include those who claim a quite distant relationship. Any relative may thus object to the use of the body for the purposes specified in the Act, and any such objection will override the consent of any other relative though not the deceased's own wishes.

Authority must not be given, nor may parts be removed, without the consent of the coroner if there is reason to believe that he may require an inquest or postmortem examination to be held; there is thus an obligation on the person who can authorise removal to obtain the coroner's consent and also on the doctor who proposes to remove parts to obtain it or see that it is obtained.

Another section of the Act removes any doubt about the lawfulness of postmortem examinations in hospitals for the purpose of establishing or confirming the causes of death or investigating the existence or nature of abnormal conditions, as distinct from postmortem examinations ordered by the coroner or carried out for teaching purposes under the Anatomy Act. Here again, reasonable inquiry must be made to ensure that the deceased had not expressed objection in his lifetime and that the surviving spouse and any surviving relative does not object. And the coroner's consent must be obtained if there is reason to believe that he may require an inquest or postmortem examination.

In view of the comprehensiveness of the new Act, the Corneal Grafting Act has become redundant and has therefore been repealed. But there is a serious scarcity of eyes for this purpose in many parts of the country, and the Government are anxious that the need for eyes for grafting should be made more widely known. A leaflet prepared by the Royal National Institute for the Blind is being sent to hospitals for display in outpatient departments, and general practitioners are also asked to make use of it.

Where are They to Go?

A recent judgment in the Court of Criminal Appeal [1] underlines what we said earlier [2] about the difficulties of securing hospital treatment for convicted persons suffering from mental disorders. Under sections 60 and 65 of the Mental Health Act, the courts may order convicted persons to be admitted to hospital instead of sending them to a penal institution, but (largely because of the security problem) hospitals are not always willing to accept such cases.

In December, 1960, a man had been convicted at Quarter Sessions, and the court made a hospital order under section 60 coupled with an order under section 65 restricting the hospital from discharging him without the consent of the Home Secretary. On admission to hospital he was examined and, treating him as a patient, the doctor came to the conclusion that there was very little sign of mental illness about him. Accordingly he left him at large to walk about the hospital as he thought fit and to work in the gardens with no physical obstacle to his walking through the gate.

Eventually the man did walk out of the hospital, but was later arrested on charges of taking and driving away a motor vehicle without the owner's consent and with dangerous driving. He was convicted and sentenced to preventive detention. It was his appeal against this sentence which provided the Court of Criminal Appeal with the opportunity of commenting on the operation of the Mental Health Act.

The following points emerge from the judgment of the Court of Criminal Appeal as given by Mr. Justice Glyn-Jones:

(1) A person subject to a hospital order under the Mental Health Act is received into hospital not as a criminal but as a patient.

(2) The convicted person must nevertheless be kept in custody.

(3) The only way to ensure safe custody is for the court to ascertain, before making the order, which mental hospital can receive the person concerned and whether this hospital has facilities for keeping patients in safe custody.

1. *Times*, Aug. 15, 1961.
2. *Lancet*, Aug. 5, 1961, p. 301.

(4) If the protection of the public demands that the convicted person should be incarcerated and there is no vacancy for him in a secure hospital, he should be sentenced to prison in the normal way, leaving it to the prison medical authorities to arrange appropriate medical treatment.

These observations were no doubt intended as guidance to lower courts, and they may result in fewer hospital orders being made. But there is little point in making orders which cannot be properly carried out, and what is really needed is a willingness on the part of the community to provide enough suitable accommodation to enable those who are adjudged by the courts to need hospital treatment to receive it instead of being sent to prison.

Mistaken Operation on Liver

A woman of 58 died after an operation undertaken for the removal of the right kidney but during which part of the liver was removed by mistake. At the inquest last week [1] a verdict of accidental death was returned after the coroner had told the jury: "There is very little evidence to show that the very experienced surgeon who carried out this operation did more than make an extraordinary mistake. Unless there is evidence of utter recklessness, you must leave it as accidental death—or the surgeon must be tried for manslaughter." The surgeon explained how, after making a posterior incision, he took the right lobe of the liver to be the kidney and began to dissect it. When he realised his mistake, his intention had been to excise the part he had cut. A pathologist said the cause of death was shock and hæmorrhage due to partial excision of the liver. The part remaining weighed $5\frac{1}{2}$ oz., suggesting that about 30 oz. had been removed.

Public Health

Influenza Vaccine

THE Joint Committee on Poliomyelitis Vaccine appointed a subcommittee to consider whether advice should be issued to the medical profession in this country on the best use of the influenza vaccines now generally available under the National Health Service. The members of this subcommittee were Sir Christopher Andrewes, Prof. G. W. A. Dick, Prof. C. H. Stuart-Harris, Prof. Wilson Smith, and Dr. G. S. Wilson. They recommended a combined influenza A and B vaccine for use in specified circumstances, and the Joint Committee on Poliomyelitis Vaccine has endorsed this recommendation.

The subcommittee did not recommend routine immunisation of all sections of the population against influenza, and they believed that the vaccine given in this way could not be expected to make a significant contribution to the control of outbreaks of the disease. Routine use of the vaccine might be indicated, however, for the protection of certain special groups in the general population:

(1) Persons with certain chronic diseases in whom an attack of influenza might aggravate their disability or prove fatal. For instance, those with the following complaints might benefit from annual inoculation with a saline vaccine during the early part of the autumn: (*a*) chronic pulmonary disease (e.g., chronic bronchitis and emphysema, asthma, bronchiectasis, pulmonary tuberculosis and fibrosis); (*b*) chronic heart-disease (e.g., valvular and hypertensive heart-disease); (*c*) chronic renal disease (e.g., chronic nephritis); and (*d*) diabetes and possibly other less common endocrine disorders such as Addison's disease.

(2) Expectant mother, whose pregnancy will extend into the winter months, particularly those with chronic lung or heart disease, might similarly benefit.

This list was not intended to include all possible disorders calling for vaccination against influenza.

In the threat of a large epidemic, such as that in 1957, persons to whom priority should be given would include nurses,

1. *Times*, Sept. 22, 1961.

hospital staff, general practitioners, persons employed in public safety, transport, or utility services, and workers in essential trades and industries where a break in continuity of production might result in severe economic loss. The subcommittee did not recommend routine annual immunisation for persons in this group.

For the present the only type of vaccine recommended is an inactivated influenza A and B saline vaccine. Because of the widespread dissemination of the Asian virus during the epidemics of 1957, 1959, and 1961, a single dose of saline vaccine containing antigen of the Asian virus, administered subcutaneously, was considered adequate.

Cholera in Hong Kong

WHEN cholera was reported last month from territories adjoining Hong Kong, plans to deal with an outbreak in the Colony were put in readiness. Production of cholera vaccine was increased and all medical institutions were warned that cases might arise. Quarantine anchorages were established to deal with boat traffic from Macao and junk and sampan traffic plying between the mainland and Hong Kong waters. Food inspections were intensified, and all water-supplies in the Colony were checked and wells in the urban area chlorinated daily. The public were advised what additional personal precautions to take.

On the evening of Aug. 15, 2 suspected cases of cholera were reported in the Colony—1 from the Kowloon public mortuary and the other from the Pok Oi Hospital in the New Territories. Both cases were bacteriologically confirmed on the morning of Aug. 16 and Hong Kong was declared an infected area. Cholera treatment and isolation units were established, additional inoculation centres were opened, and all medical and health staff were redistributed to deal with demands for inoculation. Cholera vaccine was distributed free to private practitioners, and large employers of labour were advised to obtain vaccine through their own doctors. Between Aug. 16 and Sept. 9, 71 primary cases of cholera were confirmed bacteriologically, 7 of which were brought in dead. Of the 64 patients treated in hospital another 7 died. Of these 7, 2 were drug addicts, 1 had a right pyonephrosis, and 1 was an old lady of 79. 23 (32·4%) of the 71 primary cases were in boat people, who form 4·4% of the population.

The policy was to isolate at the quarantine centre all immediate contacts of confirmed cases. On arrival at the centre, each person was given 1 ml. of 8000-million-strength cholera vaccine, and a rectal swab was taken. A further 52 bacteriologically confirmed infections without clinical symptoms were thus detected. Once the need for quarantine and investigation of contacts was explained, those concerned cheerfully accepted the situation.

The strains of vibrio isolated and typed have been of the Ogawa type, and no fully hæmolytic strains have yet been found. Fresh subcultures have been sent to reference laboratories and preliminary reports confirm these findings.

The response of the public to the inoculation campaign was unexpected and almost overwhelming. Starting on Aug. 14, groups most at risk were given priority and mass campaigns began in the islands, the New Territories, among the boat people, and in the waterfront areas where two days later the first cases were confirmed. By Aug. 17 some 130,000 persons had been inoculated and in the next five days a further 1,149,600 inoculations had been done at the Government centres. During the same period vaccine sufficient for 329,000 persons was issued free to non-Government agencies and private practitioners. Up to and including Sept. 7, 2,132,050 persons had been inoculated from all sources, out of a total population of 3,128,000.

There was no " explosion " of clinical cases as was anticipated. The largest number on any one day was 8. During the first eleven days 50 clinical cases were bacteriologically confirmed. The next twelve days produced 21 cases, with two days without a new case. It is too early to forecast what will happen, but sporadic cases must be expected to arise for some time.

In England Now

A Running Commentary by Peripatetic Correspondents

Finland may be part of Scandinavia; but after a three-month tour of hospitals there and in Denmark, Sweden, and Norway I find that I think of it as quite different from the other three. The architecture, though splendid, has that heavy semi-Russian quality that makes you feel you have put at least a toe-cap into the East. The scenery, while not unlike that of many parts of Sweden, exaggerates the flat lake-and-forest motif to a degree that stirs the spirit of Sibelius within you. The place-names are so completely extraordinary. It is astonishing to think that I have actually been to Järvenpää and to Riihimäki (and that I have some idea of how to pronounce them), that Tapiola now means more to me than just a title on a gramophone record. Yes, it is the language that, in the last analysis, defeats familiarity. As usual, I found that I knew, by the end of the second day of my stay, the equivalents of please, thank you, and beer, but it is difficult to progress beyond that. Here, for example, are the opening words of the Finnish national railway time-table:

> Kaikki rautatieliikennepaikat, jotka on avattu henkilöliikenteelle, ovat *rautatieliikennepaikkojen aakkosellisessa luetolossa* . . .

It makes one wonder how the Finns manage to communicate their thoughts to each other at all. Any impression, however, that Finland is a country that is culturally or otherwise backward would be false. The people are delightful, the arts are flourishing, the economy is sound, there is a genuine democracy, the status of women (always a good measure of a nation's wellbeing) is high, and as for the hospitals—I would say in all sobriety that the finest hospitals I have seen in Europe are to be seen in Finland: not only architecturally, but in terms of progressive modernity. Here you can see intensive-care units in action, double-corridor wards in profusion, and a vast efficient aseptic-looking central laundry that serves the whole of the 5000 beds in the city of Helsinki.

* * *

Most people have heard of the flourishing group (or colony?) of specialist bacteriologists called the Staph Club. Less well known is a huddle of London histopathologists called COSH: the exact meaning of the initials escapes me, but it claims to be a small and efficient club intended for use rather than display. But I understand that only determined action by the chairman of the British Association for Cancer Research (assembled for its second meeting at the Middlesex and engaged in drawing up its constitution) prevented a strong and persuasive group of dissidents from convincing members that a more appropriate titular arrangement would be the Cancer Research Association of Britain.

* * *

Some of your readers may like to know that even in such an out-of-the-way community as ours, there a clear relationship between environment and neurotic ill-health.

The highest incidence is among the Italian women, whose husbands are almost all farmers or farm labourers. These women live in a " little Italy " transplanted into the bush, speak no English, and are never alone, being immersed in children, aunties, and greatnephews—in a word they are every one of them cherished members of a tightly knit and friendly kinship group. They are *very* neurotic.

Next come the English-speaking farmers and their wives. They live close to the land, lead useful lives creating valuable produce by the work of their hands. They are busy, usually prosperous; the climate is equable, prices not too unstable; their children are healthy, and they mostly have cars to go and see their neighbours, telephones to talk to them, television sets to watch after milking. They too are pretty neurotic.

The hospital gardener, who has tended roses for the last nine

years and doesn't even know who his official boss is, he has tension headaches.

The railway workers, who live in shacks and who are shifted about all over the State every two years, often at a few days' notice; the mill workers with their ridiculously unsafe workplaces; the school-teachers, with classes of 50 screaming polyglot infants; the bank managers during the credit squeeze—they're mostly pretty stable types.

Topsy-turvy, Sir? But this is the Antipodes.

* * *

Last week three agents attacked patients in my practice: a pair of secateurs, a teaspoonful of honey, and a parrot. Which would you think the most dangerous? Where would the lesions be?

On Monday afternoon a calm voice on the telephone asked if I could come over at once. "I've had rather a nasty accident with the secateurs." I followed the trail of blood upstairs to the bathroom. Surprisingly, she was not at the basin with her injured hand, but sat with skirt raised over the bath. The secateurs had been left open, points upward, in her weeding basket. She had tripped and sat down heavily and with regrettable accuracy. The eight stitches were nothing to the discomfort from those two huge wounds during the next week.

On Wednesday evening a frantic Welsh voice said: "Will you come over at once—Dai is choking." I found him on a kitchen chair very near to death. His eyes bulged and his face had the deep colour of a ripe Victoria plum. He was making desperate efforts to breathe and was frightened—since he was having no success. Ten minutes later, looking pink and less frightened, he told me between coughs how his son had taken up bee-keeping. The first jar of honey had arrived that day and he had thought to sample just a teaspoonful. As I looked at the jar of clear brown fluid I thought how viscous it was—a bit like that stuff we used to drop over the back of the tongue for bronchograms.

On Friday an amused voice told me the tale of the parrot. The lady had seen me earlier in the week with "earache". I had traced it to the temporo-mandibular joint but I was ætiologically evasive. "I've just realised how I strained my jaw," she said. "It was Joey." It seemed that my patient and Joey (an elderly parrot well known to me) had discovered a mutual delight in competitive mimicry. Playing his ace, Joey had ended the game with a hair-raising sound picture of cats fighting. In trying to trump it the lady had opened her mouth just a tiny bit too wide. A surprising injury—at the age of seventy-two.

* * *

I think my fellow peripatetic was ill-informed and over-energetic to make up a new limerick.* The one on which I was brought up ran:

A lad was gestating a thesis
On dysdiadochokinesis.
But he said, "It is clear,
With exams drawing near,
It was only a pseudocyesis."

When I quoted it to a friend last week he offered another version—written, he fancied, by Dr. H. C. Chapman, for a prize in the *University College Hospital Magazine* about 1936. It went much as follows:

Each time he flew into a fury a
Schizophrenic of Upper Manchuria
Developed hemiparesis,
Dysdiadochokinesis,
And hæmatoporphyrinuria.

* * *

During my evening ward round I stopped at the bed of a rather deaf lady who had had a cholecystectomy the same morning. She opened a bleary postoperative eye and, at the same time, I held up for her to see the large solitary gallstone which had been found in her gallbladder. "Oh dear, doctor," she moaned, "I couldn't possibly swallow that without a glass of water."

* Dr. Jackson gives *his* limerick on p. 775.—Ed. L.

Letters to the Editor

MANAGEMENT EFFICIENCY IN THE HEALTH SERVICE

SIR,—Mr. Burrough (Sept. 16) questions my basic premise that the objective of the Health Service is the provision of the best medical care that the nation can afford. The objective he proposes—"the provision of the care that the health of the people requires"—is the one contained in the Beveridge report and in the N.H.S. Act itself. But unfortunately it cannot be used as a criterion for deciding how much money to spend on the Health Service, because the concept of requirement for medical care is relative, and largely subjective.[1]

How many hospital beds are required for children having their tonsils removed? A low figure will be supplied by those doctors who consider most tonsillectomies unnecessary. How much anticoagulant is required to give long-term anticoagulant therapy to patients with coronary-artery disease? Not very much, according to the cardiologists who think that such therapy has little or no value. After childbirth, does a mother require to be in hospital for three weeks (as in the past), for ten days (as in England today), or for five days (as in the U.S.A.)? Do Health Service patients really require telephones in the wards? In some countries they would be considered a luxury, in others a necessity.

Since no objective answer can be given to the question of how much medical care the health of the people requires, the Government have to find other criteria for determining expenditure on the Health Service. When I suggest that the primary criterion should be the size of the national income, I do so because observation shows that expenditure on health by a nation depends very largely on the size of the national income.[2] High-income countries spend more and low-income countries less. As national income rises, expenditure on medical care tends to rise as fast or slightly faster, however it may be financed.

I agree that when I say that the objective should be to provide the best medical care the nation can afford, I beg the questions of what is the best medical care and what can the nation afford. I avoid defining what is the best (which would be a futile task) by assuming that no country is able to have as good a health service as it would like, and that at any given moment the citizens would like it to be better. We are therefore left with the question of what a nation can afford.

Any decision here is of course a value judgment: one person may say we can afford 3% of national income, another person 4%, and another 5%. I have therefore tried to answer the question pragmatically. Over the last twenty-five years (apart from the war) Britain has spent roughly 4% of its national income on medical care, while latterly many other Western nations have also been spending $3\frac{1}{2}$% to $4\frac{1}{2}$%. It therefore seems reasonable for the Government to allocate, say, 4% of national income to the service. After a few years they could review the situation; and, if they decided to alter the percentage, the people would be immediately aware of this because the size of the proposed Health Service tax would be changed. Violent changes in the proportion are, of course, liable to lead to predictable difficulties, as I have already explained.[2]

The Health Service is already being financed roughly in this way. On July 26 the Chancellor of the Exchequer announced that the growth of current expenditure (at con-

1. Seale, J. R. *Lancet*, 1960, 1, 1399.
2. Seale, J. R. *ibid.* 1959, ii, 555.

stant wages and prices) on the N.H.S. would be planned at $2^1/_2\%$ per year for the next four years.[3] As this is about the rate at which the national income has been rising in recent years, the decision to limit N.H.S. expenditure to a constant proportion of national income for the next few years *has, in fact, already been made.* I am only proposing that this decision should be carried a stage further.

My suggestion for a special Health Service tax to replace money from general taxation, National Insurance health contributions, and the rates is not so revolutionary as Dr. Galloway (Sept. 2) seems to believe.

Most prosperous Western countries now have schemes for providing medical care to most of their citizens financed by compulsory payments. Great Britain is unique in obtaining from general taxation so high a proportion of the funds for financing medical care. Other countries such as New Zealand, Norway, and Western Germany pay for the public medical service almost entirely by social-security taxes which are independent of other Government funds, and are paid by employers and employees in proportion to income. The result has been much more freedom for the medical profession, and for individual initiative at community level, than has been possible in Britain.

Richmond,
Surrey. J. R. SEALE.

POSSIBLE ABSENCE OF ESSENTIAL HYPERTENSION IN TWO COMPLETE PACIFIC ISLAND POPULATIONS

SIR,—How welcome is a carefully executed study of the arterial pressure of a whole population in a primitive Pacific Island, such as reported by Dr. Maddocks (Aug. 9), and confirming the findings previously described by Lovell, Maddocks, and Rogerson [4] on less complete populations. My congratulations to him.

I would, however, like to question whether his observations are easily explained by the absence of a discrete group qualitatively different from the rest of the population and termed essential hypertension. Presumably this group would be absent because the alleged specific gene was absent, or some environmental factors necessary for its full display were absent.

Maddocks thinks his addition of a hypothetical curve for hypertensives to the actual curve for Gilbertese gives a frequency distribution curve like the one we found at the same age in a population sample in this country. I fear that I cannot see the similarity between his theoretical combined curve and our actual curve. There are some bumps on both and both are positively skewed. When the two curves are superimposed (fig. 1) it is seen that our curve tends to be shifted to the right. The Gilbertese curve for women aged 50–59 is not unlike that for our women aged 30–34 and 35–39 which I give for comparison (fig. 2). The difference between the Gilbertese and the

3. *ibid.* Aug. 5, 1961, 324.
4. *Aust. Ann. Med.* 1960, **9**, 4.

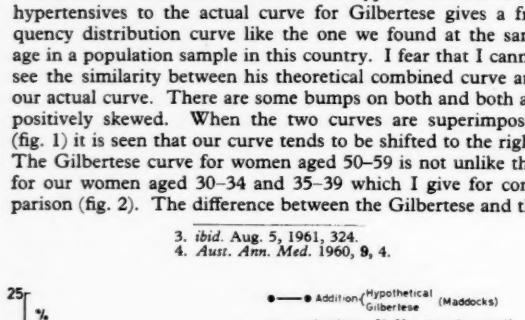


Fig. 1.

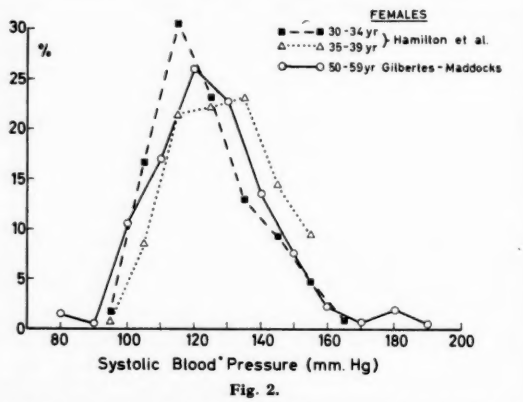


Fig. 2.

Paddington women aged 50–59 would seem to lie in a tendency for the bulk of the Paddington subjects to have higher pressures. In other words, Dr. Maddocks' second suggestion that there are factors tending to raise blood-pressure in middle age which operate more strongly in Paddington than in the Gilbert Islands is in simple agreement with the facts.

I would like to question the practice of inventing a curve, then combining it with a real curve and concluding that because the combined curve resembles a given real curve therefore that the latter is constituted in this way. Obviously if you know your stuff you can invent a hypothetical curve which, combined with a real curve, will match almost any other real curve. Maddocks' combined curve does not match the real curve, but it could have done so, had a suitable hypothetical curve been chosen.

This seems a suitable opportunity to point out what a curve actually composed of two genetically different populations looks like. We showed [5] that the frequency distribution curves of the first-degree relatives of propositi with essential hypertension were shifted to the right at all ages, as compared with those of relatives of controls. If you wish to believe the dominant-gene hypothesis, then the former represent the curves for folk half of whom had the gene, and the latter curves for folk none of whom had the gene, plus the addition to each of a fraction representing gene frequency. If you combine the two populations you should get a real bimodal curve composed of two genetically different populations. The two curves for the two sets of relatives are shown for females aged 30–39 in fig. 3. The curves are similar in shape but different in position. Adding them produces the curve in fig. 4. This is a composite curve representing two actual populations in equal numbers. Note that it has only one peak. To identify the two populations in this curve would require, I suspect, considerable mathematical genius, and perhaps one or two assumptions.

To put the record straight, it has never been our

5. *Clin. Sci.* 1954, **13**, 273.

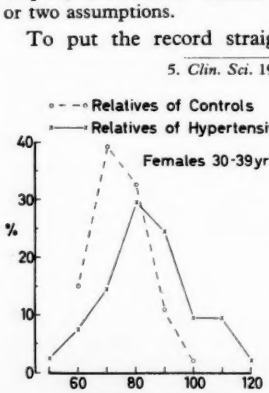


Fig. 3.

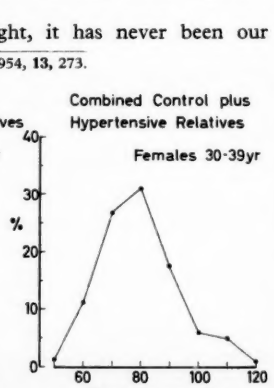


Fig. 4.

contention that the population is homogeneous genetically as regards arterial pressure. What we deny is that there is any good evidence that it consists of only two parts, those with the gene for essential hypertension and those without it. The evidence, with which I will not again bore your readers, suggests that the inheritance of blood-pressure, like height, is graded and polygenic. There are not just two kinds of people genetically as regards blood-pressure; there are more than two, and how many we cannot tell. In the same way there are not just two kinds of people genetically as regards stature, the tall and the short; there are more than two, and how many, once again, we cannot tell.

What Dr. Maddocks has clearly shown is that the rise of blood-pressure with age is different in the Pacific islanders. This is a most important finding, because he has established it with some firmness though the rapid decline in numbers in the older age-groups as compared with similar British samples—i.e., of Miall and Oldham [6] has to be taken into account. There is a good deal of evidence that the rate and pattern of rise with age is determined rather by environmental than by genetic factors. If a search were concentrated on what these factors may be and how much each contributes, then progress will be made. It will not be made by inventing hypothetical populations.

Oxford. GEORGE PICKERING.

MEDICINE AND HISTORY

SIR,—If Dr. Todd (Aug. 26) reads the works of Hippocrates, of Galen, of Aretaios, of Sydenham, of the great British clinicians of the 17th century and of so many other heroes of our history, he will find in them not dogma and authoritative opinions but the strictest methods of observation, of experimentation, and of logical critical reasoning. In fact it is the physicians—the Ancient Greek physicians—who introduced into the world what we know today as the scientific method.

Further, the reading of the case-histories of the physicians of the past will show that, long before the 20th century, they were far from helpless to influence the course of disease. It is true that they could not cure diabetic coma, or pernicious anæmia, or severe infections, but regarding all these other diseases that constitute such a great part of human pathology they were as competent—if not more competent—than we are now. With a fresh mind, unburdened by technical knowledge, the greatest amongst them had an intuitive understanding of the human constitution and of the constitutional powers of resistance to disease. The correction of environmental factors did not escape their keen vision. Their knowledge of human nature combined with their deep philosophical culture and the conviction of the sacredness of their calling gave them a powerful psychotherapeutic influence, rarely found in our days of "analytical" psychotherapy. Reading their case-histories and the testimonies of their contemporaries shows that they were able to cure many, restore them to health and to the zest for life.

It is sad to read of the belittlement of our great ancestors, of those who, surrounded by so many obstacles, have trodden their laborious path and followed it on to its high and bright consummation of our contemporary science. History is now at the centre of our medical work. History means in Greek "investigation" and not "chronicle". We cannot understand our medical problems except in the light of their historical origin and development. The most perfect form of knowledge—to repeat the words of Benedetto Croce—is historical knowledge. This history of medicine has, however, to be studied carefully, with the intellectual honesty of the scientist and the general view of the philosopher. Such a study will show that History of Medicine, far from being a chronicle "of follies and errors", is the study of the progressive development of the noblest conquest of the human mind.

London, W.1. A. P. CAWADIAS.

6. *ibid.* 1958, **17**, 409.

ADVERTISEMENTS FOR HEALTH

SIR,—Many of us, like Dr. Mullins (Sept. 16), are perturbed at the excesses of some advertising, especially in so far as it affects health. I believe however that we are not likely to improve the situation so long as we are indiscriminate in our attacks, and careless in our accusations. Unless we believe that all advertising is misleading and that its total abolition is a practical and likely outcome of our agitation, we should do far better to concentrate on those specific examples which really are potentially harmful. We can then expect at least a large number of manufacturers and advertisers to support rather than to resist a campaign for more stringent legislation and particularly for more vigorous enforcement.

I hope that Dr. Mullins, whose writings I always read with admiration, will forgive me if I say that she is less than careful in some of what she writes about slimming foods. She confuses the *fact* that the so-called "high-fat" diet really does lead to weight reduction, with the *hypothesis* that it does so by some peculiar metabolism of fat. There is no doubt that the obese lose weight on the "high-fat" diet, which is restricted in carbohydrate and unrestricted in fat and protein. As we have shown,[1] this comes about simply because the diet is low in calories; it is not in fact a high-fat diet, and should be called the low-carbohydrate diet rather than the high-fat diet.

Many others besides myself are now recommending the "high-fat" diet in the treatment of the obese, since it turns out to be practicable, sociable, and readily adopted as a permanent eating habit.[2] This being so, it is logical that we should be able to recommend to our patients foods such as bread substitutes which have been especially prepared so as to contain far less starch than bread contains. Here again, then, our job should be to press for action which will prevent misleading claims for those bread substitutes which contain as much starch as bread.

I have already suggested at the B.M.A. annual meeting in 1958 [3] that one way of dealing with the problem of claims for slimming would be for some body, such as the B.M.A., to issue a seal of approval for acceptable products. Another way would be for some responsible body to organise an exhibition of slimming foods and devices, simply but forcefully annotated. But there may be better ways of helping the public to differentiate between sense and nonsense in the vast and growing slimming business. I for one would lend my wholehearted support to any project which would reasonably do this.

Queen Elizabeth College, London, W.8. JOHN YUDKIN.

SIR,—Dr. Mullins has excellently put into words thoughts which have been troubling most doctors and many others besides.

The influence of advertising on our whole way of life must be profound, and we seem to have reached a point where "invention is the mother of necessity" is the modern restatement of an old proverb.

Although, as Dr. Mullins states, good work is being done by

1. Yudkin, J., Carey, M. *Lancet*, 1960, ii, 939.
2. Yudkin, J. *ibid.* p. 1302.
3. See also *Roy. Soc. Hlth J.* 1959, **79**, 1.

small societies, such as the Consumers' Association (whose recent assessment of baby foods is a model of fair scrutiny), more attention should be paid to the study of the social effects of advertising.

The business of advertising poses problems which are moral, philosophical, and religious, as well as economic and political. These deserve serious and detached consideration.

Perhaps one of our home-made millionaires could be persuaded to found a university chair of sales resistance. He might prefer to call it by some other name, and so long as the professor were allowed to do his work in peace I should not quibble over his title.

Upper Sydenham,
London, S.E.26. JOHN BURKINSHAW.

THE PHARMACEUTICAL PERSUADERS

SIR,—In many ways your anonymous correspondent of Aug. 19 has examined the industry-medical relationship thoughtfully and helpfully. It is certainly important that the physician in practice or in academic work fully understands the commercial nature and function of our industry. We are frequently surprised that some defenders of the profession see the need to remind their brethren so often of this obvious fact.

But I am concerned that the constructive possibilities of this article will be buried by its cynicism and glaring distortions. On p. 423, your correspondent makes the unqualified statement that pharmaceutical advertising makes full use of "taking facts out of context and misapplying them." I am not so naïve as to deny that this has happened. But your correspondent is grossly unfair in his blanket condemnation of pharmaceutical advertising on this score. Inquiry will confirm, I am confident, that distortion and misquoting are the exception and not the rule.

Next I challenge your correspondent to produce the pharmaceutical house organ that does, as he says, "attack, deride, dissuade, and perform any number of miracles of modern advertising." I am aware of many outstanding publications issued on a regular basis by or under the sponsorship of pharmaceutical firms and have yet to see examples of the abuse he cites.

Finally, I urge your readers not to be misled by his allegation that "many, if not most, medical congresses are now organised and supported by the pharmaceutical industry." Many medical meetings are in a sense "supported" partially by revenue from pharmaceutical exhibits, but it is absurd to imply that the firms "organise" the meetings. Occasionally a drug firm will sponsor a meeting devoted to a field of research interest or to a particular compound under study, but rarely indeed is the sponsorship of such meetings in any way hidden.

In short, I think your correspondent has let his rhetoric run away with his facts. And I do not believe there is room for exaggeration and distortion between those in medicine and those in industry who wish—as we in the United States most certainly do—to preserve a progressive, vigorous system of medical care free from Government domination.

Smith Kline and French Laboratories,
Philadelphia,
Pennsylvania. G. F. ROLL
Director of Public Relations.

MALIGNANT MELANOMA

SIR,—Although in 1959 there were only 381 deaths from malignant melanoma in England and Wales, your leading article of Sept. 9 opens up an interesting subject because so many of these cases (about 80%) have their origin in long-existing pigmented moles.

In my lectures to the lay public when speaking of cancers of the skin, I mention that there is a very rare kind, which I call "black cancers". I explain that although they are very rare they sometimes start in a black raised mole, and for that reason it is advisable for anybody with such a mole to consult their doctor as to whether it should be "cut out" but not treated by cautery or other means. You quote Ewing and Powell as saying this is bound to result in many unnecessary operations. Who is to judge that the removal of any individual mole was unnecessary, as nobody can make an accurate prognosis of the future behaviour of such a mole by looking at it?

The late Dr. Margaret Tod wrote [1] that if a patient asks to have a mole removed he must be strongly advised to leave it alone, but that if he insists the operation must be as radical as if the lesion showed signs of active growth. Surely a simple excision together with a centimetre surround of healthy skin and fascia, should be sufficient. To wait until the mole shows signs of active growth and the survival rate drops to 25% does not seem to be a good example of "preventive medicine".

Cancer Information Association,
Oxford. MALCOLM DONALDSON.

SIR,—The following case may be of interest since it illustrates some points raised in your leading article of Sept. 9.

A married woman of 45 (2-para) had a pigmented mole since birth on the left lower eyelid. She noticed in June, 1947, that it was getting slightly larger. She was referred to an ophthalmic surgeon who did a local excision and plastic repair. There was a recurrence at the operation site 4 months later, and on Dec. 22, 1947, a surgeon excised the small tumour together with the preauricular glands and subcutaneous tissues. She made a satisfactory recovery but a left facial palsy developed. She was seen periodically until 1950.

She was next seen on Feb. 23, 1957, when she complained of a small swelling in the left epitrochlear region which was tender and painful. She had noticed it for about a week. It felt like an enlarged gland not attached to any of the muscle groups. There was no noticeable enlargement of the axillary glands. The patient was immediately referred to the special hospital where she was seen before. A left axillary and epitrochlear dissection was performed there on March 11. The pathological examination of the removed gland proved that it was a malignant melanoma.

Three more small tumours appeared on Aug. 7 in the right loin, right scapular, and left gluteal regions. They were dissected at the same hospital on Aug. 12. They contained deposits of large pleomorphic, anaplastic, and hyperchromatic cells—an appearance consistent with metastatic deposits of malignant melanoma. She left hospital on Aug. 24.

Two more small tumours appeared in the abdominal wall on Sept. 9 and the patient began to complain of persistent headaches, nausea, and vomiting. She developed diplopia on Oct. 2 and pain in the left shoulder and arm. She became gradually more and more unsteady. She was readmitted on Oct. 12, and became irrational, confused, and uncooperative, probably because of cerebral metastases. She died on Oct. 26.

It is interesting that a mole which was benign for 45 years suddenly developed malignant changes resulting in local spread only. This was probably caused by some premenopausal hormonal activity. Surgical dissection halted its spread. 10 years later the spread became hæmatogenous and more virulent, probably owing to a more intense postmenopausal hormonal activity which determined the increased malignancy. This sequence of events supports the view expressed in your leading article that a malignant melanoma may be in some degree hormone-dependent and that its prognosis is better in women before than after the menopause.

London, S.E.25. A. FRY.

1. *Lancet*, 1944, ii, 532.

INFLUENCE OF REDUCTION OF SERUM LIPIDS ON PROGNOSIS OF CORONARY HEART-DISEASE

SIR,—Dr. Oliver and Dr. Boyd (Sept. 2) say that the third principal objection to their study is that giving a potent œstrogen "cannot be regarded as a physiological means of reducing serum lipids in men". It appears that neither the patients nor their wives were told that the treatment was entirely experimental and would almost certainly cause enlargement of the breasts and probably cause impotence, which might be permanent. Should not this study therefore be described as unethical rather than not physiological?

Farnham, Surrey. JOHN W. TODD.

*** We showed Dr. Todd's letter to Dr. Oliver and Dr. Boyd and their reply follows.—ED. L.

SIR,—Dr. Todd draws attention to ethical problems in relation to clinical trials. It was in recognition of these problems that all the men selected to receive ethinyl œstradiol were told that they would receive a female sex hormone for the next few years in the hope that it would reduce the risk of a further heart attack. They were also told unambiguously and in non-technical terms that this treatment would produce gynæcomastia and reduce potency. Incidentally, Sir, Dr. Todd misquotes us: we said that "there are three principal criticisms of this study"—*objection* is his word.

The treatment was not described as "entirely experimental" since this was not so. Before this trial commenced, the effects of ethinyl œstradiol on the serum lipids had been intensively investigated and clearly defined. It was also known that the presence of elevated serum lipids favoured the development of coronary heart-disease. There was adequate evidence for implementing a clinical trial of the effect of reduction of serum lipids on the prognosis of coronary heart-disease, and seven years ago there was no alternative to œstrogen therapy. We believe, therefore, that this trial, which has given instructive results, was a logical development and should not be regarded as unethical. When an exploratory clinical trial gives negative results, it may be more liable to be labelled unethical. Had œstrogen treatment clearly prolonged life this accusation might well not have been made.

M. F. OLIVER
Edinburgh. G. S. BOYD.

LANGUAGE: THE LOST TOOL OF LEARNING

SIR,—It seems that Boileau's ideas, quoted by Sir Francis Walshe last week, were already foreshadowed in the 13th century by Robert Grosseteste, the medically minded Bishop of Lincoln. As I recall it, his terse Norman-French phrase ran: "Ki ben sayt ben peut decte"—Who knows well can say well.

Bushey Heath, Hertfordshire. F. CAMPBELL ROSE.

HELLENOMANIA-HELLENOPHOBIA

SIR,—A valuable result (for me) of your allowing me to put my opinions in print is that I have learnt a lot. I am very grateful for Dr. Langford's reminder that the Greek for blood is αιμα, and to Dr. Woods for correcting my impression that a phenomenon is something extraordinary. A glance at Fowler would have prevented this error—which he calls "a sin against the English language".

To answer Dr. Woods' other points: (1) I am sorry if I implied that "trabecula" is plural, for I was trying to point out that some Latin singulars are confusingly like other Latin plurals; (2) it may be easier to "get the gist" of a medical passage in Spanish than of the same passage translated into German, but disastrous errors of interpretation may follow missing a negative, mistaking a tense, &c.

The limerick I referred to appeared in the *London Hospital Gazette* in or about 1949. If my memory is less at fault than usual, it was anonymous, and ran something like this:

A medico writing a thesis
Found his wrist movement going to pieces.
There's a lesion, poor feller,
In the site cerebellar
Causing dysdiadochokinesis.

I have not got the reference at hand, and apologise to the author and editors if I have misquoted. I enjoyed your peripatetic correspondent's limerick on the same topic.

Faulkner Hospital, Boston, Mass. DAVID M. JACKSON.

*** Readers will not be surprised to learn that two more limericks appear on p. 771.—ED. L.

SIR,—In his cogent and witty article of Sept. 2, Dr. Jackson overlooks one point of some interest. Graeco-Latin hybrids may not be barbaric; most of us can frame such words as "bicycle" and even "television" without blenching. But they may nevertheless lead to unexpected confusion.

Dr. Jackson mentions the word "radiological" with approval. Since *radius* is a well-known Latin word and *logos* a well-known Greek word, the meaning of "radiological" might be thought to be beyond doubt. But there is also a very common Greek word *radios*. (Classicists may remark that it was generally written with a subscript iota and that the 'r' was aspirated, but neither iota nor aspiration would necessarily be carried over to a derived English word.) It means "easy". Once this is realised, "radiology" acquires a galaxy of possible meanings. The kindred term "radiobiology" may readily be interpreted as "the science of taking life easy".

M.R.C. Radiobiological Research Unit, Harwell, Berks. H. S. MICKLEM.

EUTHANASIA

SIR,—Most senior general practitioners, I imagine, must once or twice in their careers have been faced with the dilemma of a dying patient, frequently of the highest calibre, requesting euthanasia ("tonight, doctor") so as to anticipate by a week or two, possibly only a few days, the inevitable conclusion of his or her illness. Our compassion and our sense of obligation to our patient (who has probably discussed the matter with us beforehand) is in direct conflict with our legal and, some would say, moral responsibility. We compromise by giving sub-lethal doses of drugs which may actually prolong the process of dying; this is called helping the patient over the last hurdle, and seems to satisfy the consciences of most doctors, despite the fact that in so doing the patient may be deprived of his personality and dignity, and die in lingering coma, an ugly caricature of a human being. In fact, "euthanasia" is frequently given, but, in my view, too little and too late.

Now that the Suicide Bill has been passed, with hardly a dissentient voice, it seems that the Legislature, at any rate, takes the view that it is no longer always obligatory to try to preserve the life of one who wishes to end it. It follows, therefore, that a doctor who accedes to his dying patient's request, acting solely from compassion, and with, of course, minimal appropriate safeguards, should have legal sanction for his action. Unfortunately,

clause 2 of the Suicide Bill makes aiding or abetting suicide (itself no longer a crime) liable to prosecution, though not without the consent of the Director of Public Prosecutions, who would no doubt withhold such consent in the case of a doctor acting in good faith.

Nevertheless, I feel that, as the law stands, Society asks the family doctor to shoulder alone too heavy a responsibility in these admittedly few, but often very poignant, deathbed requests for euthanasia.

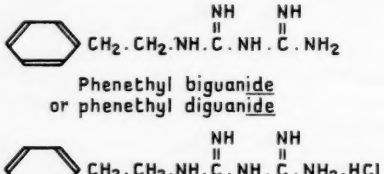
Leicester. MAURICE MILLARD.

BIGUANIDE OR DIGUANIDE?

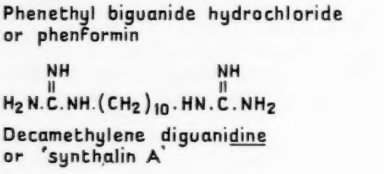
SIR,—Professor Butterfield and his coauthors, in their paper of Sept. 9 on the action of phenformin, state that this is a *bi*guanide and not a *di*guanide (their italics). But are these two terms not synonymous? Whether the Latin or the Greek prefix is employed the meaning remains the same. Synthalin with two guanidines joined by a chain of methyl groups is a diguan*idine*. In phenformin the two guanidines coalesce with the elimination of NH group, and it is a diguanide (or biguanide). As some authors describe phenformin as a diguanide and others as a biguanide some confusion may arise. This could be avoided if the distinction between guanidine and guanide is borne in mind. Incidentally proguanil hydrochloride is a biguan*ide*.

Victoria Infirmary, Glasgow. IAN MURRAY.

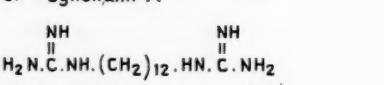
SIR,—Thank you for showing me Dr. Murray's letter. He is quite right and we are obliged to him for drawing attention to this point. It might help your readers to give the relevant formulæ:



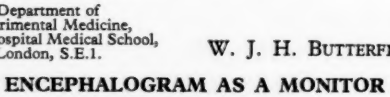
Phenethyl biguanide
or phenethyl diguanide



Phenethyl biguanide hydrochloride
or phenformin



Decamethylene diguanidine
or 'synthalin A'



Dodecamethylene diguanidine
or 'synthalin B'

Department of Experimental Medicine, Guy's Hospital Medical School, London, S.E.1. W. J. H. BUTTERFIELD.

THE ENCEPHALOGRAM AS A MONITOR OF STATUS EPILEPTICUS

SIR,—It is always illuminating to read an article from Oxford, and Dr. James and Dr. Whitty's account (July 29) of the uses of electroencephalography as a monitor in status epilepticus was no exception. On reading Dr. Rollason's letter of Aug. 19, suggesting the use of thiopentone drip to control status resistant to the usual treatment, I was reminded of a case some three years ago, which was treated by a combination of E.E.G. monitoring and thiopentone drip.

A very muscular young man, whose post-traumatic epilepsy had been controlled hitherto with phenytoin sodium and phenobarbitone, was admitted to the neurosurgical unit at Bristol in status epilepticus, and first attempts at control were ineffective. The day after his admission I gave him a deep anæsthetic for just over half an hour, after an induction dose of thiopentone of about 750 mg. had been necessary to stop his fits completely. He had been having almost continuous right-sided fits involving face, arm, and leg; he was apparently at least partly conscious; and the fits spread from time to time to include the whole body. He was much congested, but not significantly cyanosed, and he was sweating.

The fits ceased after induction, and anæsthesia was maintained with nitrous oxide, oxygen, and chloroform. But as soon as he began to recover, the fits returned with undiminished severity. An intravenous drip was set up, and a further 250 mg. of thiopentone were given into it.

The saline drip was replaced by a 2·5% solution of thiopentone, given at a rate sufficient to remove the eyelid reflex. At first, intermittent injections of 5% thiopentone were necessary to abort movements and to limit the heavy fluid input. Under these conditions, anæsthesia was very light, and convulsions were absent.

At this stage the E.E.G. showed an epileptogenic focus in the left frontotemporal region, which was giving rise to frequent large spikes and waves.

If the thiopentone drip was slowed, and the patient became lighter (sluggish eyelid response), the frequency of the abnormal wave patterns increased, and then similarly shaped and synchronous discharges began to appear in the opposite frontotemporal region. At this time, or immediately after it, fits would begin in the right arm, and were arrested by giving more thiopentone.

When the drip-rate was increased to deepen anæsthesia, spread into the opposite cortex became intermittent, and then ceased, and the frequency of the abnormal waves in the left hemisphere became less. This state was achieved at a level of anæsthesia only just below that at which a sluggish eyelid reflex was present.

After these observations were made, he was given a faster drip, and gradually the abnormal patterns from the left frontotemporal electrodes became more and more infrequent, until by about 6 P.M. that evening the E.E.G. pattern from both frontotemporal zones appeared to be similar, and essentially normal, taking into account the thiopentone narcosis. The drip was then slowly reduced in rate, and about an hour after the pattern had become virtually normal, no abnormal waves re-emerged.

The dose of thiopentone used over approximately 8 hours was no less than 15 g. He was, however, conscious and mentally normal next morning, and was well thereafter, until he was readmitted in status some months later. This extraordinary dose of thiopentone followed a short general anæsthetic, which had included chloroform and other drugs in his previous treatment.

The combination of thiopentone drip and E.E.G. monitoring was equally effective in his second episode, though far less thiopentone was needed. The value of the monitoring was that it indicated beyond doubt when the source of the fits had become quiescent, and avoided repeated trial removal of narcosis.

Admittedly patients who remain in status epilepticus die of exhaustion and respiratory failure, and not of the effects of cortical delirium; and where a patient has been treated by conventional methods without success, and is becoming exhausted, treatment by curarisation and artificial respiration would seem a very sound method, though these cases must be rare, as Dr. James and Dr. Whitty suggested.

Department of Anæsthetics, St. Bartholomew's Hospital, Rochester, Kent. PETER L. F. MORTIMER.

DOCTORS FOR THE FORCES

SIR,—Your very thoughtful and fair leading article of Sept. 23 appears none too early. The Government departments who are now the main employers for doctors may each find their medical commitments widening while the available manpower seems every day to diminish. With Parliament soon to be recalled the Government ought to find out why young people are not attracted into our medical services.

You have given six or seven reasons why medical practice in the Armed Forces proves unattractive to young doctors. Another surely just as important is the poor state of the Services' public relations. Advertising has been tentative, clumsy, or smug. Service medical journals are weak, commanding neither support nor respect. Small wonder that too few doctors have lately joined the Army, which has the most urgent problem by far. If the R.A.M.C. is to improve its recruiting impact by better publicity, it must first try to discover why students and young graduates do not wish to join. This could be quickly done by an attitude survey. Without the foundation of such research, recruiting efforts may well continue to be a dismal waste of public funds.

SERVICE CRITIC.

FURTHER ABNORMALITIES OF THE X CHROMOSOME IN PRIMARY AMENORRHŒA OR IN SEVERE OLIGOMENORRHŒA

SIR,—In a study of the chromosome constitution in primary amenorrhœa or severe oligomenorrhœa we have observed three chromosome abnormalities: one partial deletion of the X chromosome (46 Xx) similar to that described by Jacobs et al.[1]; one mosaic of normal and 46 Xx cells; one 46 XX/47 XXX mosaic. The second and third cases seem to be the first reported.

CASE 1.—The patient, aged 27, came under observation because of primary amenorrhœa. She menstruated only once at the age of 19 after receiving chorionic gonadotrophin. Her mother menstruated at the age of 18, but unfortunately could not be examined. There is no other unusual family history. The patient, 5 ft. 3 in. (1·60 m.) tall, was sexually underdeveloped with small breasts and scanty pubic and axillary hair. The vulva, the clitoris, and the vagina were normal. The uterus was underdeveloped and no endometrium could be withdrawn with Novak's sound. No malformations (such as webbing of the neck or cubitus valgus) were present, but she had many nævi. Hormone excretion was as follows: 17-ketosteroids, 6 mg. per 24 hours; follicle-stimulating hormone, 25–50 units, more than 50 units, and 5–25 units on three consecutive assays. Laparotomy showed the ovaries to be small, spindle-shaped, nacreous, and with a vascular pattern similar to that in gonadal dysgenesis. The ovarian wall was fibrous but thin with primordial follicles underlying it. No follicular cysts or corpora albicantia, old or recent, could be seen. A wedge resection of the ovaries failed to restore menstruation.

In buccal mucosa smears the sex-chromatin body was present in about 15% of the cells. A fragment of the abdominal aponeurosis was set up in culture tubes.[2] Chromosome counts in 25 cells and chromosome analysis in 11 cells were consistent with a chromosomal abnormality similar to that described by Jacobs et al.—namely, the absence of one chromosome in the X-size range and the existence of one supplementary chromosome similar to number 16. These findings are interpreted as being due to the deletion of the major part of the long arm of one X chromosome.

CASE 2.—A woman of 22 sought advice because of severe oligomenorrhœa and sterility. She menstruated for the first time at the age of 13½ and had had only 6 periods since—in 8½ years. She had been married for two years and had never been pregnant. Her appearance was that of a normal female, with well-developed breasts and broad hips. Her external genitalia and vagina were normal, the uterus being a little undersized and the ovaries rather larger than normal. Her temperature

1. Jacobs, P. A., Harnden, D. G., Court Brown, W. M., Goldstein, J., Close, H. G., MacGregor, T. N., Maclean, N., Strong, J. A. *Lancet*, 1960, i, 1213.

2. Lejeune, J., Turpin, R., Gautier, M. *Rev. franç. Ét. clin. biol.* 1960, **5**, 406.

Dispersed chromosomes and karyotype in case 1.

graph showed one single peak. Her vaginal secretions were hypoœstrogenic. The F.S.H. excretion values lay between 5 and 25 units. These findings were consistent with the diagnosis of Stein-Leventhal syndrome and a laparotomy was advised. This showed two oversized, white, nacreous, smooth and hard ovaries. Histological examination showed no evidence of corpora lutea or albicantia, but rather small cystic follicles, and a few follicles with hyperplasia of their theca folliculi, were present. The wall of the ovaries was thick with primary follicles in its deeper layers. A wedge resection of the ovaries was performed and, shortly after, regular menstruation with corpora lutea was restored.

Cytogenetic studies showed the sex-chromatin body in 35% of the cells and the chromosome constitution to be a mosaic of normal cells and of cells with a karyotype identical with that described in case 1. Of 17 cells analysed, 9 belonged to the first type and 8 to the second.

CASE 3.—The patient, aged 28, menstruated only once at the age of 21, although pubic hair had appeared normally at the age of 13. Her breasts were well developed. She was somewhat overweight (69 kg., height 5 ft. 5 in. [1·65 m.]), and she had abnormal hair on the face, chest, and abdomen. Her external genitalia were normal, and the uterus was in retroversion, anteflexion, and dextroposition. The ovaries were hard, smooth, and three times the normal size. Vaginal secretions were hypoœstrogenic. A small biopsy fragment showed the endometrium to be at the non-secretory stage. The temperature curve was low and flat. The F.S.H. excretion values lay between 5 and 25 units. The clinical picture suggested the Stein-Leventhal syndrome. Laparotomy confirmed the existence of two enlarged ovaries, and the histological findings were as in case 2. A wedge resection of the ovaries induced, within 30 days, menstruation which was maintained regularly with a corpus luteum.

A single nuclear sex body was present in 30% of the buccal cells, and two such bodies were present in 2–3% of cells. Chromosome analysis of mitotic fibroblasts displayed a 46 XX/47 XXX mosaic, 11 analysed cells being of the first type and 9 of the second.

The first case is very similar clinically to the only other case we know of—namely, the first case of partial deletion of the X chromosome described by Jacobs et al.[1] (In a second case Jacobs et al.[3] report another type of deletion, that of the short arm of the X chromosome.) The karyotypes are also very much alike. We did not feel, however, that the nuclear sex bodies were somewhat smaller than in normal females. Yet the subjectivity of such an estimate cannot be denied. Notwithstanding the chromosome findings, on clinical grounds alone—we are inclined to classify case 1 as an intermediate form between gonadal dysgenesis and the Stein-Leventhal syndrome, either as a mild form of the first or as a severe form of the second. The reasons for doing so are the small ovaries and their anatomical picture as well as the failure of the operation to restore menstruation. On the other hand, we believe cases 2 and 3 are typical of the Stein-Leventhal syndrome. The fact that case 2 is a mosaic of normal and Xx cells could support the hypothesis that case 1, consisting of only Xx cells, is a severe form of the Stein-Leventhal syndrome. Yet the great difference between the chomosome findings in case 2 and case 3 (46 XX/47 XXX) leads us to believe that the Stein-Leventhal syndrome could actually be the phenotypical expression of different chromosome constitutions.

Jacobs et al.[3] draw attention to the fact that no mosaics have been reported in which the " stem-lines differed only in the morphology of the chromosomes " and hence favour the hypothesis that the morphological abnormalities of the X chromosome arise before fertilisation rather than after. Our case of XX/Xx mosaic therefore gives a new turn to this discussion and suggests that a morphological abnormality of the X chromosome (or any chromosome) may also arise after fertilisation. Regarding our XX/XXX mosaic, we do not know of any other such case. The loss of an X chromosome in an early stage of development of an XXX zygote would seem the most reasonable way to explain it.

Full reports and discussion of these cases will be published elsewhere.

We wish to acknowledge the technical assistance of Miss M. Roubin. This work was supported by the Institut National d'Hygiène (Prof. L. Bugnard) and the U.S. Public Health Service (grant M.39.21).

Clinique de Génétique Médicale, Hôpital des Enfants-Malades, Paris.
J. DE GROUCHY
MAURICE LAMY.

Service d'Endocrinologie et Gynécologie Clinique, Hôpital Necker, Paris.
H. YANEVA
Y. SALOMON
A. NETTER.

3. Jacobs, P. A., Harnden, D. G., Buckton, K. E., Court Brown, W. M., King, M. J., McBride, J. A., MacGregor, T. N., Maclean, N. *Lancet*, 1961, i, 1183.

CLEAN HANDS

SIR,—I am sorry to say it has come to my notice that there was an error in my letter of June 10. In the last line of the third paragraph the strength of the solution of chlorhexidine (' Hibitane ') in spirit should be 0·5%, *not* 0·05%.

Oxford. J. C. SCOTT.

CEREBRAL FAT-EMBOLISM SUCCESSFULLY TREATED BY CARBON-DIOXIDE INHALATION

SIR,—Dr. Broom (June 17) reported the successful treatment of cerebral fat-embolism by carbon-dioxide inhalation. He also mentioned the possibility of treating fat-embolism with heparin.

The idea of using heparin in fat-embolism derives from the clearing effect of heparin in lipæmia. But an additional factor in fat-embolism is that coagulation is affected. There have been many reports of profuse petechial hæmorrhages. There have also been reports of intracapillary fibrin deposits. Cammermeyer's case [1] is an example of this. We ourselves have observed diffuse hæmorrhage from the stomach and intestinal tract.

Experimental work has shown that disturbances of blood-coagulation can occur in fat-embolism [2]; Penick et al.[3] observed such disturbances after the injection of tissue extracts and concluded that they consisted in intravascular coagulation and resultant consumption of clotting factors. Lasch et al.[4] have observed a similar consumption of clotting factors in different illnesses and successfully treated it with heparin. Heparin can also lessen the tendency to hæmorrhage in experimental fat-embolism.[5] This confirms the results of Gardner and Harrison,[6] who were able with heparin to avoid hæmorrhage as a cause of death. That results have not been more successful is not surprising, since heparin dilates the blood-vessels and this increases the amount of fat carried from the lungs to other organs. In addition, heparin increases capillary permeability, which in turn, because of increased œdematous imbibition, has an unfavourable effect on tissue around the fat-occluded vessels.

H. H. SESSNER
G. SCHÜTTERLE
D. STUMMEYER.

Medizinische Universitätsklinik, Heidelberg, German Federal Republic.

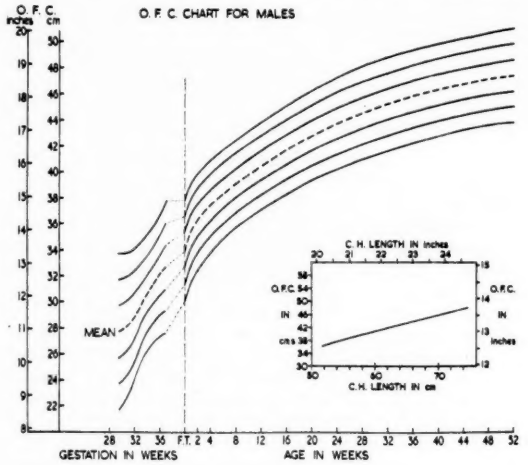
1 Cammermeyer, J. *Arch. Path.* 1953, **56**, 254.
2. Sessner, H. H., Schütterle, G., Stummeyer, D. *Dtsch. Arch. klin. Med.* 1961, **207**, 177.
3. Penick, G. D., Roberts, H. R., Webster, W. P., Brinkhouse, K. M. *Arch. Path.* 1958, **66**, 708.
4. Lasch, H. G., Krecke, H. J., Rodriguez-Erdmann, F., Sessner, H. H., Schütterle, G. 7th German Hæmatological Congress. Wiesbaden, 1961.
5. Sessner, H. H., Schütterle, G., Stummeyer, D. 8th European Hæmatological Congress. Vienna, 1961.
6. Gardner, A. M. N., Harrison, M. H. M. *J. Bone Jt Surg.* 1957, **39B**, 538.

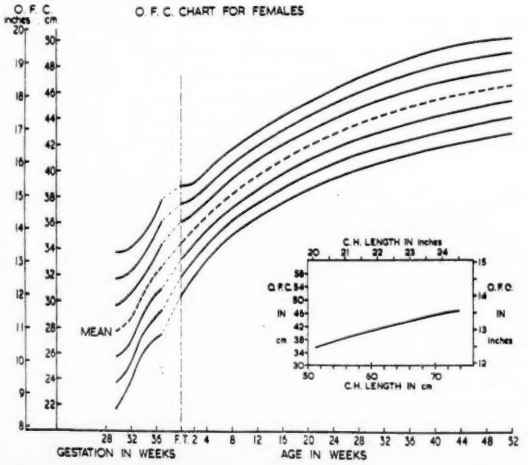
MEASUREMENT OF THE OCCIPITOFRONTAL CIRCUMFERENCE IN CHILDREN

SIR,—Serial measurements of the occipitofrontal circumference are routinely taken in pædiatrics where cerebral irritation, subdural hæmatoma, spina bifida, meningitis, or other causes of possible skull expansion in infancy are suspected or already diagnosed. Comparable, accurate tapemeasures are needed which should not cause cross-infection (particularly important in maternity hospitals); and the measurements are of greater value if they can be plotted serially on a standard curve.

Tapemeasures are often inaccurate when new; and if of linen, they stretch. Thus short-term serial measurements on an individual baby with different tapemeasures may mean little. This difficulty may be partly overcome by using identical flexible steel measures; but antiseptics used to clean them often spoil the spring return mechanism.

Disposable paper tapes are very useful, provided they are accurate. Those we describe below cost approximately 1*d.* for three. They are of good quality paper, the graduations are in inches (subdivided in eighths); and the tapes are accurate to within 1–2 mm., not only over 30 in. but also from inch to inch.





Occipitofrontal circumference (O.F.C.) mean curve and three standard deviations above and below. C.H.: crown-heel; F.T.: full term.

They are easily coiled up. We put them routinely in the small locker of our neonatal cot unit.[1]

The measurements are recorded graphically for each sex. The figures have been prepared from data for premature babies[2] and for Edinburgh infants in the first year of life.[3] These show the mean curve and three standard deviations above and below it. The time-scale extends from twenty-eight weeks' gestation through full term to age one year. The insert enables the observer to see whether a given skull circumference is disproportionate to the mean crown-heel length. These curves are produced by a xerographic technique on graph paper measuring $9^1/_2$ in. × 8 in. and can be incorporated in case-notes. They cost £4 15*s.* for 500 (just over twopence each).

The disposable tapemeasures are obtainable from Berwick's Toy Company, Ltd., Birkenhead Road, Wallasey, Cheshire, and the graphs from Mackenzie & Storrie, Ltd., 28–32, Coburg Street, Leith, Edinburgh, 6.

Department of Child Life and Health,
University of Edinburgh. JAMES W. FARQUHAR.

MUSHROOM POISONING

SIR,—As one who has eaten fungi for thirty years without poisoning himself, I should like to support the views of Dr. Lloyd (Sept. 23). The species that he mentions are a great addition to one's diet, but I wish he would tell me how best to cook *Amanita rubescens* because our efforts do not seem to do it justice. In return I will show him a way to improve the flavour of Boletus.

Dr. Bickford is right, of course, in saying that a volva and ring are found in the genus Annelaria, but the black spores prevent confusion with Amanita. We thought that your diagram of *Amanita phalloides* was a very good one, provided that one remembers that rain may wash the white patches off the cap.

It is, of course, essential to know the species before one eats it, but the few poisonous ones are not difficult to recognise.

St. Helier Hospital,
Carshalton, Surrey. C. P. PETCH.

Obituary

ROBERT YELVERTON STONES

O.B.E., M.C., M.D. Lond., M.R.C.P., F.R.C.S.E., D.P.H., D.M.R.E.

Dr. Stones died on Sept. 16 at Mengo Hospital, Kampala, of which he was for many years medical superintendent.

He was born in 1881 at Wisbech. He qualified from the London Hospital in 1907 and, after taking the F.R.C.S.E. in 1910, he sailed for Africa in 1911 as a missionary of the Church Missionary Society. He first worked at Iyi Enu Hospital in Nigeria and in 1913 was transferred to Old Cairo Mission Hospital in Egypt. During the 1914–18 war he was commissioned in the R.A.M.C., and served in the Near East and in German East Africa. He was awarded the Military Cross. At the end of the war, he began missionary work again in Tanganyika, and gave outstanding service in the famine at Dodoma in 1919. From Dodoma he went to Maseno in Kenya, near Lake Victoria, where he founded a hospital with Red Cross funds.

In 1924 he went to Uganda and joined Dr. (afterwards Sir Albert) Cook at Mengo Hospital, Kampala, the mission hospital which Cook had founded in 1897. Here Stones worked till he retired, latterly as medical superintendent, and he was appointed O.B.E. in 1938. In 1939 he returned to England, but he could not reconcile himself to

1. Farquhar, J. W. *Lancet*, 1960, ii, 1152.
2. Ellis, R. W. B. *Arch. Dis. Childh.* 1951, **26**, 411.
3. Thomson, J. *ibid.* 1956, **31**, 382.

a quiet life at home. He again joined the R.A.M.C. and was in Malta during the siege. He stayed on for a time and was in charge of the King George V Hospital for Merchant Seamen. After the death of his wife, he felt the urge to return to his work in Africa, and he revisited first Nigeria and then Uganda. Though now in his seventies, he resumed work at Mengo Hospital for a time. Latterly he concentrated on ophthalmology, always one of his great interests, and he was seeing patients at his eye clinics until the onset of his last illness.

W. R. B. writes:

"A brilliant student, Stones gained one degree or diploma after another during his periods of home leave. He had been a vigorous tennis-player and swimmer, and was a pioneer motorist. Quiet and reserved, and a most modest man despite his professional distinctions, he only wished to use his talents for the greatest good wherever he was. He was keenly interested in the advancement of African doctors and longed to see them taking their place in the different hospitals in which he had served. A true and humble Christian, his uncomplaining patience in his last illness was characteristic, and it was fitting that he should end his days in the country for which he had done so much, and in the hospital he had served for so long."

GLYNFAB CADIFOR DAVID EVANS
M.B., B.Sc. Wales, D.M.R.

Dr. Glyn Evans, director of the radiotherapy services of the United Cardiff Hospitals and the Welsh Board of Health, died in Cardiff on Sept. 18.

He was born at Port Talbot and qualified from the Welsh School of Medicine in 1942. Soon after qualifying he decided to specialise in radiotherapy, and he took the D.M.R. the same year. Later he became assistant radiotherapist at the Christie Hospital, Manchester, assistant medical director of the Sheffield National Centre of Radiotherapy, and radiotherapist to the Nottingham and Notts radiotherapy centre at the General Hospital, Nottingham. He returned to Cardiff in 1947 and had worked there since.

L. C. R. writes:

"At the Whitchurch Hospital in Cardiff, Glyn Evans organised and built up a highly efficient department equipped with the latest apparatus where he and his staff did first-class work for patients from a wide area. His helpful experience was ever at the service of his colleagues, who valued his opinion and advice, and nothing was too much trouble for him if it might help them in their problems. He was a good teacher and popular with students. He stagemanaged their Christmas plays and joined them in many of their social activities. He was honorary president of the Medical Students' Club for 1953–54. He was a tall good-looking man with a ready and kindly smile and an attractive personality. At the service held in Llandaff Cathedral on Sept. 21 many friends, colleagues, and students gathered to pay their last respects to him. He will long be remembered both for his personal qualities and for his work for his school and hospital."

Dr. Glyn Evans leaves a widow and four young daughters.

Prof. RAFFAELE BASTIANELLI

P. M.-B. writes:

"In your obituary of Raffaele Bastianelli no mention was made of his distinguished brother Guiseppi who did pioneer work on malaria and who died last year at the age of 94. Some sixty years ago both brothers were frequent visitors at Sir Patrick Manson's house in Queen Anne Street. I was always told that they were inseparable, and both were pupils of Marchiafava in whose laboratory (as you said) Raffaele worked for seven years."

Notes and News

THE DOCTOR IN THE COMMUNITY

A CONFERENCE on the Training of the Doctor for his Work in the Community was held in Edinburgh on Sept. 21–29 by the European region of the World Health Organisation. On the opening day, Dr. Richard Scott, director of the general-practice teaching unit, Edinburgh University, remarked that specialisation not only produced channels along which the patient must travel in search of care, but also imposed on the doctor a challenge to develop skills and techniques of consultation and of working with others in order to provide comprehensive diagnostic and therapeutic services. A new subject advanced not always by splitting into two new subjects, but often by narrowing of the area of the subject, which sloughed off much of its content into the undifferentiated field of general practice. Owing to this constant feed-back from hospital medicine to general practice, to some extent what yesterday was hospital practice became general practice today. But general practice was distinguished from hospital practice by its growing preoccupation with the psychosocial component of the patient's environment. Dr. Scott and his colleagues, in a study of 32,418 consultations in their practice, had found that just over 10% involved direct action (dressings, injections, minor surgery, &c.); in 38% prescriptions were given, and in 13% certificates; while 72% involved advice (diet, hygiene, smoking, &c.), explanation (health and disease), discussion about social services or work or personal relationships, or therapeutic listening. General practice was the area where society and medicine met: in a general-practitioner service the community had an eloquent and effective means of telling medicine how it could best meet the community's needs.

THE NEW SUICIDE ACT

UNDER the Suicide Act 1961 attempted suicide is no longer a criminal offence. This amendment implies that in future it is to be regarded entirely as a medical and social problem and the Minister of Health has asked hospital authorities, local authorities, and general practitioners to ensure that these patients get the help they need. They will often be sent to casualty departments for emergency physical treatment, but before discharge they should receive psychiatric investigation and where necessary inpatient or outpatient treatment. Their general practitioner should always be given full information. With the patient's agreement the local-authority services should also be asked to help. General practitioners should consider whether a patient who has attempted suicide should be sent to hospital for psychiatric treatment even if he does not need physical treatment. They should also not hesitate to ask for the help of the local-authority mental health services.

CURRENT HOSPITAL EXPENDITURE

LONG-TERM planning is to be introduced for current as well as capital hospital expenditure, and the Minister of Health has asked hospital authorities to submit not only estimates for next year but also forecasts for the two following years.[1] Later he hopes to extend this "forward look" to cover five years. The level of expenditure will be governed by the Chancellor of the Exchequer's announcement [2] that the rate of growth of current expenditure on the health and welfare services as a whole will be planned for the next four years at about $2^1/_2$% per annum (in terms of constant wages and prices). In view of the need to expand the community-care services, the Minister plans to provide an increase of 2% for hospital current expenditure. Because of the savings achieved by "improved efficiency and organisation" he has felt justified for the first time in asking boards to meet the cost of general price increases during the current year from the existing allocations without reducing the level of their services. (The provision made for hospital current expenditure is about £445 million and the price increases to be absorbed may be over £3 million.) The

1. H.M. (61) 90.
2. See *Lancet*, Aug. 5, 1961, p. 324.

Minister will, however, provide extra money to meet the cost of salary and wage awards which have come into force since the existing allocations were calculated.

THE WORLD'S DENTAL SCHOOLS

A NEW W.H.O. publication [1] gives particulars of education in dentistry in 70 countries, describing the administration, conditions of admission, curriculum content, and examination procedures of the dental schools, and regulations governing licences to practice. This should prove a most useful work of reference for all engaged in dental education.

It also contains figures giving the ratio of population to registered dentists in each country; and these will be of wider interest, since they show remarkable variations, even between countries in Western Europe. Comparison of some of these ratios may suggest fruitful lines of inquiry to dental research-workers. Why, for example, do the Norwegians, with 1 dentist for 1500 inhabitants, require the services of, proportionately, more than three times as many dentists as the Dutch (1:4700)? This discrepancy can hardly be the result of the Dutch community expecting and demanding a much lower standard of dental care than do the Norwegians. Each community is sophisticated enough to attach proper importance to dental health, and it seems reasonable to conclude that the proportionately much more numerous dental profession in Norway reflects the Norwegian population's greater need for treatment. The reverse might have been expected since the Dutch are renowned for their addiction to sweets and biscuits, whereas the Norwegians, even if they do not entirely subsist on the "Oslo breakfast", have a reputation for abstemiousness in this respect. The anomaly may be due to the presence in the Dutch environment of some factor preventing deleterious diet from having its usual effect on dental health. If such a factor does exist and could be isolated, many uncertainties in our understanding of tooth decay might be cleared up.

It is not surprising that most economically underdeveloped countries have too few dentists and too few dental schools. Rapid expansion of training facilities is not possible; and no doubt the authorities in these countries will watch with interest our experiment in using dental ancillaries, in the hope that a similar scheme may help them.

University of Sheffield

A course on the assessment of the development of the infant and pre-school child is to be conducted by Prof. R. S. Illingworth and his colleagues from Nov. 23 to 25. Further information will be found in our advertisement columns.

Royal College of Surgeons of England

Sir Clement Price Thomas will give a Thomas Vicary lecture on Thursday, Oct. 26, at 5 P.M., at the college, Lincoln's Inn Fields, London, W.C.2. The subject will be Vicary amongst his contemporaries.

Royal College of Obstetricians and Gynæcologists

At the meeting of council on Sept. 23, with Mr. A. C. H. Bell, the president, in the chair, D. R. Cairns and M. H. V. Young were admitted to the fellowship and the following to the membership:

F. D. Adey, Farid Akasheh, J. H. Andrew, Mukundadas Auddy, Amy Pushpam Augustus, C. A. Barbaro, Subodh Chandra Basak, Monish Kumar Basu Mallik, R. P. Beck, Vishnuprasad Motiram Bhatt, Saroj Kanti Bhattacharjee, David Bower, E. J. Brown, Gillian J. Browne, J. G. Bundey, A. P. Camilleri, Chun-Hian Chong, O. McK. Coltman, C. C. Curlewis, Biswanath Das, J. J. De Wet, G. H. H. Dwyer, R. P. Dyer, Harold Edelstein, J. J. Eisenberg, J. H. N. Ferris, D. L. Flax, R. J. Fothergill, W. A. Fraser, Simon Friedman, R. F. R. Gardner, A. G. Gordon, G. S. Hall, Abubakr Mustapha Hassim, G. D. Henderson, J. B. Hill, E. L. Holland, J. K. Houston, Christine M. Hyslop, John Hughes, Florence Suhasini Iswariah, H. F. Jolly, D. H. Jones, John Kelly, H. R. Klein, Catherine M. Lamplugh, R. D. Leckie, M. R. Lee, Ngan Ngieng Ling, Gareth Lloyd, Therese Ti-Li Lu, W. W. McDougall, J. A. McGarry, H. A. H. Melville, Krishna Chandra Mitra, Subimal Mukerjee, Sharangdhar Dinkar Mulye, R. N. Munday, Vidya Sagar Nagpal, B. R. Neill, D. Y. Nelson, Wendy E. Noble, E. R. Parry, Masihur Rahman, E. H. Ritchie, Shirley B. Robertson, Patricia G. Roose, Dilip Kumar Sarkar, Alicon V. Scott, Samir Prasad Sen, Sudhindra Kumar Sen, Janet Shaw, Jack Shirazi, G. O. Smith, D. B. Spanton, F. M. Spence, Daniel Sullivan, Kyu Kyu Swe, K. W. Tang, Arumugam Tharmaratnam, James Vernon-Parry, G. P. Walker, B. G. Wren, Edward Yenson.

The annual dinner was held in London on Sept. 22.

Mr. Enoch Powell, the Minister of Health, who proposed the toast of "this yet youthful college", spoke of its "restless spirit of enthusiasm and initiative". He cited its investigation into the maternal death-rate as an admirable example of self-criticism which could profitably be copied by much of the National Health Service, and he praised its survey into human relations in obstetrics, started by Sir Andrew Claye, the immediate past president of the college.

In his reply, Mr. Arthur Bell, the president, described the college's first year in its new "house"; in particular two committees had been formed, one to study the coordination of obstetric services in the Commonwealth, and another to look into the need for more maternity beds and the desirability of general-practitioner maternity units in local hospitals. He congratulated Sir John Peel on his new appointment to the Royal Household, and expressed regret over Miss Mallon's retirement after 32 years' service as secretary of the college since its formation.

By way of comparison with human obstetrics, Mr. Bell related that the college had recently taken a neighbourly interest in a confinement at the Zoological Society. The mother, an orang-outang, had firmly despatched her inquisitive husband in the last month of her pregnancy, and she had held the keeper-accoucheur's hand during labour; then, when her infant was safely delivered, although it was sturdy, she had promptly administered mouth-to-mouth respiration.

Mr. Ian Jackson, the retiring honorary secretary, welcomed the guests; and Sir Arthur Porritt, president of the Royal College of Surgeons of England, responded.

College of General Practitioners

South West England Faculty Board.—Dr. R. N. Curnow will give a Gale lecture on Saturday, Oct. 7, at 8 P.M., at the Town Hall, Truro. He will speak on trends in the mental health services.

British Medical Association

This Association's lecture-discussion series for 1961–62 will begin on Thursday, Oct. 19, when Prof. H. J. B. Atkins and Prof. Ralston Paterson will speak on the treatment of carcinoma of the breast. Other speakers in the series will be: Nov. 23, Sir Denis Browne (early diagnosis of orthopædic abnormalities); Feb. 15, Prof. J. T. Ingram (management of infantile eczema); and, March 29, Mr. Lawrence Abel (earlier cancer diagnosis). All the lectures will be given at 5.30 P.M., at B.M.A. House, Tavistock Square, London, W.C.1.

Biochemical Society

A meeting of this society is to be held, jointly with the British Biophysical Society, on Thursday and Friday, Oct. 5 and 6, at the School of Pharmacy, Brunswick Square, London, W.C.1. The subjects for discussion will be the physical chemistry of phospholipids, and phospholipids and sulpholipids. An ordinary meeting of the Biochemical Society will be held on Saturday, Oct. 7, at 10 A.M., at the Westminster Medical School, S.W.1.

World Health Organisation

Under the chairmanship of Dr. L. Molitor, the eleventh session of the W.H.O. Regional Committee for Europe, held at Luxembourg from Sept. 12 to 15, was attended by representatives of 27 countries of the European region.

Dr. Paul van de Calseyde, regional director, in a report on the first ten years of the regional office, spoke of the changes in the priorities given to European health problems. Whereas immediately after the war the main task was the control of communicable diseases and the reorganisation of health services, today there are other problems such as accidents, the ageing of the population, the preponderance of cardiovascular diseases and cancer among the causes of death, and the lack of nurses. These are the problems that W.H.O. is tackling in Europe.

Dr. M. G. Candau, director-general of W.H.O., appealed to the countries of Europe to increase their aid to the underdeveloped countries of the other regions. As an interim measure it was essential that Europe should open wide the doors of its training centres to students of the emerging countries, helping them to resolve their difficulties of adjustment to new conditions, and that it should be generous in providing the professors and personnel needed by those countries.

1. World Directory of Dental Schools. Geneva: World Health Organisation. 1961. Pp. 228. 25s. Also published in French. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

National Association for Mental Health

A conference on the need for cooperation in special services for the child delinquent is to be held by this Association on Wednesday, Nov. 15, at 10 A.M., at Friends Meeting House, Euston Road, London, N.W.1. Further particulars may be had from the conference secretary of the Association, 39, Queen Anne Street, W.1.

British Hospitals Contributory Schemes Association

This Association is to hold a conference on Thursday, Oct. 12, at 2.30 P.M., at the Cliffs Hotel, Blackpool, when Lord Cohen of Birkenhead will give an address.

Education, Training, and Employment of the Mentally Handicapped

The European League of Societies for the Mentally Handicapped is to hold a congress on this subject from Oct. 2 to 4 in London and from Oct. 5 to 6 in The Hague. Further particulars may be had from the secretariat, 11, Southampton Row, London, W.C.1.

American Hospital Association

At a meeting of the Association this week in Atlantic City, a distinguished service award was to be presented to Dr. E. M. Bluestone, the former director of Montefiore Hospital, New York. The honorary membership of the Association was to be conferred on Dr. G. E. Godber.

Gairdner Foundation

The five medical research workers who will share this Canadian Foundation's awards for 1961 include Sir Russell Brock and Prof. J. H. Kellgren.

Fertility and Reproduction

The Lalor Foundation offers awards for research on "the fundamental biochemical and physiological mechanisms concerned with fertility and the early stages of reproduction in various forms of life". Fuller understanding, it is hoped, will increase the possibilities of biological regulation and control.

The awards, of up to 8000 dollars per year, are open to all nationalities; but preference will be given to younger members of university and college staff, with an upper age-limit of 41. The Foundation also grants postdoctorate summer or short-term fellowships at the Marine Biological Laboratory at Woods Hole, Mass., or elsewhere. Its address is 4400, Lancaster Pike, Wilmington 5, Delaware, U.S.A., and the last day for receiving applications (in the prescribed form) is Jan. 15, 1962.

A service for doctors is to be held in All Souls Church, Langham Place, London, W.1, on Sunday, Oct. 22, at 11 A.M. Mr. A. C. H. Bell, F.R.C.O.G., and Dr. Kenneth Robson will read the lessons. Doctors who wish to reserve seats for the service should write to the church secretary, who will also issue tickets (*7s. 6d.*) for a buffet lunch which is to be held at the Royal Society of Medicine after the service.

The London Group of the Anglo-American Medical Society will hold its first meeting on Friday, Oct. 6, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, at 8 P.M., when the guest speaker will be Mr. A. Dickson Wright.

A meeting of the North of England Otolaryngological Society is to be held on Saturday, Oct. 7, at 2 P.M., in Wakefield.

Rehearsals for the London Medical Orchestra began again on Sept. 28. They take place at Rutherford School, Penfold Street, N.W.1, every Thursday at 7.45 P.M. There are vacancies in all parts and anyone who is interested should write to the secretary, Dr. H. Engel, at 40, Warrington Crescent, W.9.

A semipermanent exhibition will be held at the Institute of Dermatology, Lisle Street, London, W.C.2, from Oct. 2 to 26, by Dr. Henry Haber on histology of normal skin.

The Digest of Statistics Analysing Certificates of Incapacity for 1957-58 covers the Asian influenza epidemic in the autumn of 1957, and includes analyses of spells of influenza and bronchitis in the period by age of claimant and area of claim, duration of spell and age of claimant, and duration of spell and area of claim. Copies of the *Digest* can be had from the statistics division of the Ministry of Pensions and National Insurance, 1, Adam Street, London, W.C.2.

Sir Derrick Dunlop has been appointed honorary physician to the Queen in Scotland in succession to Sir Stanley Davidson, who has resigned and been appointed an extra physician to the Queen in Scotland.

On Sept. 21, Dr. Victor Lucas was installed as one of the first two freemen of Farnworth, Lancashire, where he had been in general practice for 40 years.

On Wednesday, Oct. 4, Prof. J. N. Davidson will give a Bottazzi lecture in Cagliari, Italy.

Diary of the Week

OCT. 1 TO 7

Monday, 2nd

ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Street, Glasgow, C.2
5.15 P.M. Dr. A. S. Parkes: Preservation and Grafting of Gonadal Tissue. (Burns lecture.)

Tuesday, 3rd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. C. Q. Henriques: Veins of the Vertebral Column and their Role in the Spread of Cancer. (Hunterian lecture.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.30 P.M. *Orthopædics.* Dr. C. Casuccio: Introduction to the Study of Osteoporosis—Histochemical, Biochemical, and Biophysical Researches on Bone Ageing.
INSTITUTE OF NEUROLOGY, Queen Square, W.C.1
5.30 P.M. Prof. Robert B. Aird (University of California): Corpus Callosum and Focal Epilepsy in Man.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. C. J. Hodson: Obstruction and Reflux in the Urinary Tract.

Wednesday, 4th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
2 P.M. Prof. Charles Gray: Chemical Pathology in Modern Medicine.
ROYAL SOCIETY OF MEDICINE
5.15 P.M. *History of Medicine.* Mr. Terence Cawthorne: Goya's Illness. Mr. Roger Brearley: Padua and the Dawn of Scientific Medicine.
8 P.M. *Surgery.* Sir Eric Riches: Conservative Surgery of the Kidney. (Presidential address.)
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Histology of Normal Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Sir Russell Brock: Chest Injuries.

Thursday, 5th

ROYAL SOCIETY OF MEDICINE
8 P.M. *Neurology.* Dr. Fergus Ferguson: A Critical Review of the Clinical Features of Myasthenia Gravis.

Friday, 6th

UNIVERSITY OF LONDON
5.30 P.M. (University College Hospital Medical School, University Street, W.C.1.) Dr. B. Berde (Basle): Physiological and Pharmacological Aspects of Oxytocin.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. John Hopewell: Kidney Storage.
4 P.M. Prof. M. D. Milne: Abnormalities of Potassium Metabolism.

Appointments

East Anglian Regional Hospital Board:

ACHAR, V. S., M.B., B.SC. Mysore: medical registrar, West Norfolk and King's Lynn General Hospital.
AL-MALLAH, Z. Y., M.B. Baghdad, D.T.M. & H., D.T.C.D.: medical registrar, Papworth Hospital, Cambridge.
DE SOUZA, L. J., M.B. Bombay, F.R.C.S.E.: registrar in thoracic surgery, regional thoracic surgery unit, Papworth Hospital, Cambridge.
GREEN, N. A., M.B. Lond., F.R.C.S.: senior surgical registrar, United Norwich Hospitals.
IZUKAWA, TERUO, M.D. Toronto: medical registrar, regional cardiac unit, Papworth Hospital, Cambridge.
KULKARNI, M. G., M.B. Nagpur, D.A.: surgical registrar, West Norfolk and King's Lynn General Hospital.
PATHAK, U. N., M.B. Punjab, M.R.C.O.G., M.M.S.A., D.G.O.: registrar in obstetrics and gynæcology, West Norfolk and King's Lynn General Hospital.
PAYNE, RUDOLPH, B.M. Oxon., D.P.M.: consultant psychiatrist, Little Plumstead group of hospitals.
SCHURECK, R. J., M.B. Queensland: registrar in psychiatry, Fulbourn and Addenbrooke's Hospitals, Cambridge.
SEN GUPTA, AMARENDRA, M.B. Calcutta: surgical registrar, Ipswich and East Suffolk Hospital.
SEN GUPTA, N. P., M.B. Calcutta: medical registrar, County Hospital, Doddington.
SHEERIN, B. J., M.B. Lond., D.A.: anæsthetic registrar, West Suffolk General Hospital.
WONG, E. M., M.B. Otago: medical registrar, Ipswich and East Suffolk Hospital.

Births, Marriages, Deaths

DEATH

CORRIDAN.—On Sept. 18, suddenly at his home, 19, Broadlands Road, London, N.6, Patrick Corridan, M.D., M.R.C.P., K.S.G.